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Catalytic Reactions of Ruthenium, Copper Nanoparticles and Rhodium Homogeneous Catalysts

루테늄, 구리 나노입자 및 로듐 균일화 촉매를 이용한 촉매반응

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김 주 현

Catalytic Reactions of Ruthenium, Copper Nanoparticles and Rhodium Homogeneous Catalysts

Supervisor: Prof. Young Keun Chung

By

Ju Hyun Kim

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Graduate School

Seoul National University

Abstract

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Ju Hyun Kim

Department of Chemistry

The Graduate School

Seoul National University

Transition metal-catalyzed catalytic reaction is one of the most fundamental processes to construct the chemical structure. Depending on the type of transition metal catalysts, the catalytic reactivity is quite different. In the field of heterogeneous catalysts, nanoparticle catalysts have been attracted due to their unique reactivity and relatively simple process for reuse. Homogeneous catalysts have many advantages such as high reaction rate and selectivity to achieve catalytic reaction of fine chemicals. Thus, developing a unique catalytic reaction with transition metal catalysts is essential to expand the field of synthetic methods.

This dissertation describes the development of catalytic reaction of transition metal nanoparticles and rhodium compounds. We discovered that ruthenium nanoparticle on non-activated charcoal is quite effective for constructing azobenzen derivatives which are useful materials of dyes and pigments. Furthermore, instead of hydrogen gas, ethanol is used as a hydrogen source. Three

different products derived from nitroarene derivatives were obtained by changing the amount of ethanol.

Copper is abundant and inexpensive metal than ruthenium metal. Using commercially available copper nanoparticles as a catalyst, cross-coupling reactions between alkyl halides with Grignard reagents were studied. The cross-coupling reaction did not require any phosphine or amine ligands and proceeded smoothly at room temperature. In particular, quaternary carbon center, being difficult to synthesize, was established in the presence of copper nanoparticle and tertiary alkyl Grignard reagents.

Alcohol is one of the most common organic compounds in our lives. It is often used as a polar solvent in chemical reactions. As mentioned above, alcohol can be employed as a hydrogen source. In addition, the role of alcohol can be extended to a carbon monoxide surrogate, a hydride-donor, and a nucleophile in the presence of rhodium catalysts. In the synthesis of esters from aryl iodides and alcohols in the presence of a rhodium catalyst and a base, an alcohol acted as carbon monoxide and nucleophile. Alcohol acted as a hydride source to form a rhodium hydride intermediate and a carbon monoxide surrogate in intermolecular carbonylative cycloaddition reactions with alkyne.

Keywords: nanoparticle catalyst, ruthenium, hydrogenation, copper, cross coupling, rhodium, alcohol, carbonylation, cycloaddition

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Chapter 1. Introduction

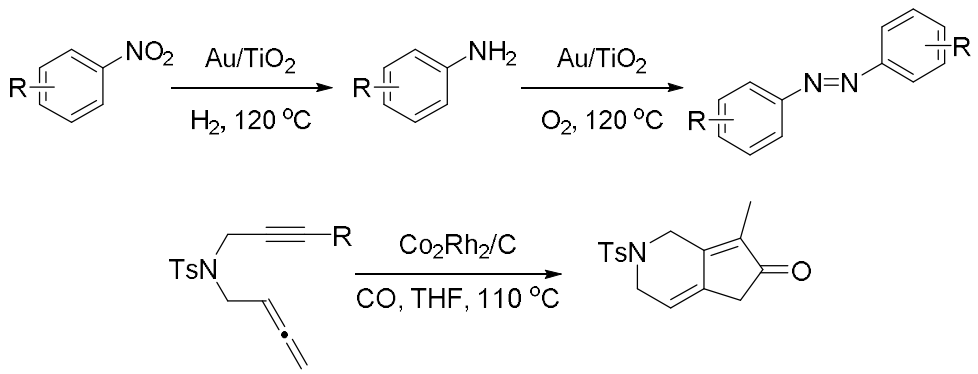
1.1. Research Background

Constructing chemical structure driven by the transition metal catalysts has been a critical position in catalysis. From the perspective of organometallic chemistry, connecting the molecules has been attracted enough to win the Nobel prize from the discovery of Grignard reagent in 1912 to the palladium-catalyzed cross coupling in 2010.[1] Thus, developing the catalyst and catalytic reactions have permeated in the synthetic chemistry field.[2] Depending on the status of catalyst, it can be divided into homogeneous and heterogeneous catalysts. Each of them has an attractive point to achieve the product. In case of heterogeneous catalysts, they are easy to separate in the reaction mixture and the reuse/recycle of the catalyst is possible. On the other hand, homogeneous catalysts have a high reaction affinity and afford relatively better selectivity than heterogeneous one. Therefore, tremendous amount of catalytic reactions using each of these have been reported steadily.[3]

Transition metal Nanoparticle-catalyzed bond forming reactions

For decades, transition metal nanoparticle is a well-known heterogeneous catalyst for numerous chemical reactions.[4] Looking back to the organic chemistry textbook, we have learned a classic heterogeneous catalytic reaction that palladium on charcoal is able to hydrogenate the unsaturated substrate in the presence of hydrogen gas.[5] As we can be seen in the case of Pd/C, heterogeneous nanoparticle catalysts typically include a transition metal and a supporter moiety. Thus, they have advantages over homogeneous catalysts, such as reusability and reactivity.[6] In early days, transition metal nanoparticle were mainly used for catalytic reactions to replace homogeneous catalyst.[7] However, as the nanoparticle catalysis has been

developed, the distinctive catalytic reactions have been reported by many research group.[8] In 2008, Corma group reported the gold nanoparticle catalyzed synthesis of aromatic azo compounds from aniline and nitroaromatics (Scheme 1.1).[9] This result showed that transition metal nanoparticle can produce a unique chemical structure.



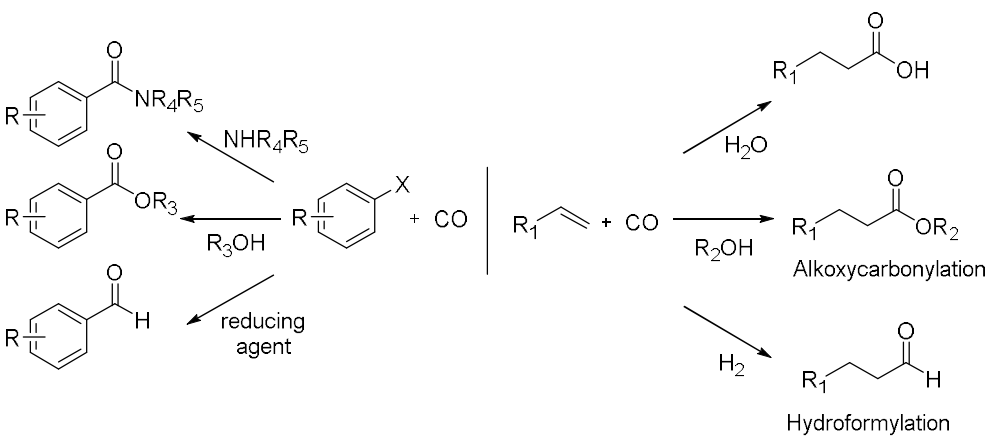
Scheme 1.1. Transition metal nanoparticle catalyzed bond-forming reactions

Our group developed a heterobimetallic cobalt-rhodium nanoparticle catalyst and published a number of unique catalytic reactions.[10] Its high reactivity in some reactions is due to the coexistence of two metals, cobalt and rhodium, in each particle. Thus, exploiting catalytic reactions using the unique property of nanoparticles is one of important arsenals in the catalysis field. During the development of nanoparticle, the use of nanoparticle catalysts without any pretreatment has emerged.[11] Most of nanoparticle catalysts should be immobilized on the supporter. This process requires additional chemical reactions.[12] Therefore, the preparation of proper nano catalysts capable of high catalytic ability and convenience is necessary for the development of nanoparticle catalysts.

Carbonylation reactions

In aspects of constructing chemical structure, carbonylation reaction is one of the most fundamental methods of organometallic synthesis for inserting C1 sources

(Scheme 1.2).[13] A variety of organic compounds such as ketones, esters, amides etc. have a C=O moiety. In general, for a carbonylation reaction to take a place, it needs (i) carbon monoxide source, generally CO gas, (ii) the substrate to be carbonylated, and (iii) a transition metal catalyst to achieve a chemical bond between substrate and carbon monoxide. Over the past decades, there have been significant progresses of the carbonylation area in terms of catalyst, substrate, and carbon monoxide sources. Earlier studies showed that metal carbonyl, such as $Ni(CO)_4$ and $Co_2(CO)_8$ were useful for carbonylation of organic compound.[14] Metal carbonyl species were quite effective for generating numerous CO-containing chemicals including carboxylic acid, aldehydes, alcohol, ketones and amides. However, the use of excess toxic metal carbonyl is less favorable.

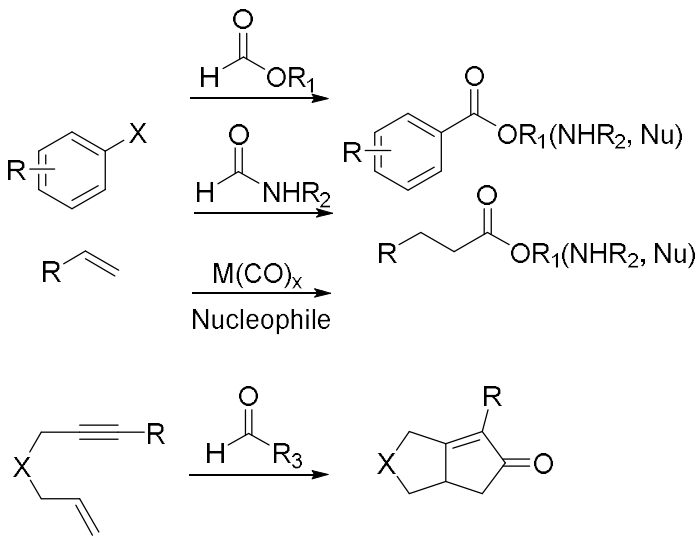


Scheme 1.2. Representative carbonylation of alkenes and aryl halides

In 1964, Tsuji et el reported a palladium chloride catalyzed catalytic carbonylation of allylic compound.[15] From this work, various transition metal catalyzed carbonylation reactions with CO gas have been developed.[16] In particular, a number of well-established carbonylations, such as hydroformylation, Reppe reaction, Monsanto process, and Pauson-Khand reaction, have been studied extensively.[17-20]

Carbonylation reaction without external CO gas

Previous studies on the carbonylation of organic compounds have shown outstanding results in synthesizing useful structures. However, most studies required high pressure of carbon monoxide.[13, 16] Carbon monoxide is a tasteless, odorless, and non-irritating, but is a highly toxic and flammable gas.[21] Intoxication of carbon monoxide and all of these properties hamper the development of carobnylation area.[21] Thus, many research groups were interested in finding nontoxic carbon monoxide sources to replace toxic CO gas.



Scheme 1.3. Carbonylation reactions without external CO gas

Over the last 30 years, considerable efforts have been devoted to exchange a carbon monoxide gas with CO surrogates.[22] There are several series of CO surrogate such as formic acid derivatives, aldehyde, and metal carbonyls (Scheme 1.3).[23-25] Recently, Beller group reported the carbonylation of alkene using CO_2 as a carbonyl sources.[26] These compounds have been extensively studied with transition metal catalysts such as palladium, ruthenium, iridium, and rhodium.[27-30] However, it is hard to represent the genuine CO surrogate because they are originated from organic compounds. Most of CO surrogates mentioned above have been extracted

in the petroleum oil. Therefore, studying more environmentally benign sources to obtain carbon monoxide are still required.

Alcohol is one of the most familiar organic compounds because of its versatility in chemical reactions.[31] From the viewpoint of chemical structure, alcohol is a reduced form of an aldehyde. Thus, if an oxidation of alcohol with transition metal catalyst is feasible, alcohol could be a powerful CO surrogate. Moreover, alcohol will be a suitable candidate of CO surrogate because it can be derived from biomass and agrofeedstock.[32] Despite their advantages of alcohol, a few studies have been reported using alcohol as a CO sources.[33] Palladium and ruthenium catalysts have been established in carbonylation of alkene or aryl halides using alcohol as a CO source.[33] However, rhodium catalysts which are favorable for the decarbonylation of aldehyde have been less studied due to the properties of rhodium-carbonyl complexes.[34] In 2010, our group developed the rhodium-catalyzed Pauson-Khand reaction using alcohol as a CO surrogate.[35] This is the first report of the Rh-catalyzed intramolecular carbonylative cycloaddition of an enyne using alcohol as a carbon monoxide source. Thus, it is highly desirable to extend the process for using alcohol as a CO source with a rhodium catalyst.

Thesis Research

Although there are plenty of reports to use transition metal catalysts, achieving the unprecedented catalytic process is a fundamental goal of extending the scope of catalytic chemistry. This redearch describes the development of catalytic system for making various chemical structures using ruthenium and copper-based nanoparticles and rhodium/ bidentate phosphine ligand catalytic system.

Chapter 2 describes the ruthenium nanoparticle catalyzed chemoselective hydrogenation of nitroarene using ethanol as a hydrogen source. By changing the

amount of ethanol, the temperature and the reaction time, three different azo, azoxy, and aniline derivatives were isolated in with high yield. This unique catalytic system is due to the relatively low reactivity of ruthenium nanoparticle over gold nanoparticle.

Chapters 3 and 4 shows that commercially available copper nanoparticle catalysts can produce carbon-carbon bond and carbon-boron bonds. Both chemical bonds are achieved in the presence of Grignard reagents and organodiboron compounds. The reaction conditions are very mild and do not need any phosphine or amine ligands.

Chapter 5 demonstrates that alcohol acts both carbon monoxide and a nucleophile in the presence of rhodium/bidentate phosphine to give aryl esters. With/without assist of aldehyde, the carbonylated compounds of aryl iodides were isolated in moderate to high yield. It breaks the concept of general carbonylation reactions through using alcohol in two important roles.

In Chapter 6, we studied the first rhodium-catalyzed intermolecular carbonylative [2+2+1] cycloaddition of alkynes with alcohol as a CO source. The alcohol performs multiple role, including generating the Rh–H intermediate, functioning as the CO source, and assisting in the isomerization of the alkyne. Alkynes can act as both the olefin and the alkyne partner in the cyclopentenone core.

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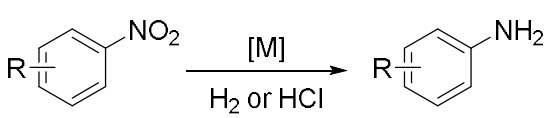
Part I. Ruthenium and Copper Nanoparticle Catalyzed Various Bond Forming Reactions

Chapter 2. Ruthenium Nanoparticle-Catalyzed Chemoselective Hydrogenation of Nitroarenes Using Ethanol as a Hydrogen Source

2.1. Introduction

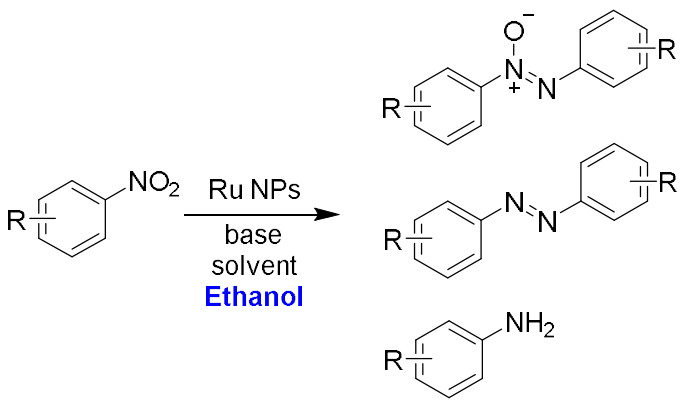
Aromatic amines are intermediates in the production of agrochemicals, pharmaceuticals, dyes, polymers, and pigments.[1] In general, aromatic amines are produced by a catalytic reduction of nitroarenes.[2] However, other reducible groups could be reduced in the hydrogenation of nitroarenes Thus, finding a catalytic system that can selectively reduce a nitro group without reducing other functional groups is a challengeable task (Scheme 2.1). In addition to hydrogen, other reducing agents have been used in the preparation of aromatic amines.[3] During the reduction of nitroarenes to aromatic amines, several intermediates such as azo and azoxy compounds are involved. Their formation in the reduction of nitroarenes results in low selectivities and low product yields. However, they are very useful compounds in synthetic organic colorants, prodrugs, and liquid crystal systems.[4] Thus, their synthesis has recently been of growing interest.[5,6] Finding mild, chemoselective, and general conditions for the reduction of nitroarenes to a range of reduction products is still of great importance.



Scheme 2.1. Hydrogenation of nitroarenes

While we were studying the application of in situ generated hydrogen (or metal-hydride) from an alcohol by catalytic dehydrogenation,[7] we discovered that the reactions of nitroarenes in the presence of a catalytic quantity of ruthenium

nanoparticles (Ru NPs) in ethanol afforded an azoxy, an azo, or an amine as a major product depending upon the reaction conditions (Scheme 2.2). Both azo and azoxy compounds are considered to be intermediates in the synthesis of aromatic amines from nitroarenes. So, both compounds could be seen in the reduction of the nitroarenes. However, isolation of one of them as a major product starting from the same reactant using the same catalyst is very rare.[8]



Scheme 2.2. Constructing azo, azoxy and amine compound with Ruthenium nanoparticle catalytic system of nitroarenes

We believe that developing a catalytic system that can produce an azo, an azoxy, or an amine as a major product just by changing the reaction conditions is an important advance. Moreover, if the system developed had the advantages of convenience and safety over the conventional catalytic system, these would be additionally attractive. Thus, the use of ethanol as a sustainable source of hydrogen and reusable nanoparticles as catalysts could be a remarkable result which may draw the process closer to the ideal of a 'Green Chemistry'. In this chapter, we present a catalytic system that can generate three reduction products of nitroarenes. General and chemoselective conditions have been developed to control the reduction outcome of nitro compounds to azoxy, azo, and amines.

2.2. Results and Discussion

2.2.1. Characterization of Catalyst and Optimization of reaction conditions

To identify the character of nanoparticle catalyst, we synthesized Ruthenium-nanoparticle catalyst. Ruthenium nanoparticles were prepared by reduction of $RuCl_3$ in the presence of ethylene glycol.[9] Figure 2.1 shows the image of the catalyst from High-Resolution TEM. Ruthenium nanoparticles supported on non-activated charcoal are formed and the sizes of the supported Ru particles are 5~7 nm. According to the ICP-AES, 16 wt% of Ru are loaded on charcoal, which is nearly the same concentration of the ruthenium used (Further characterizations can be found in the Supporting Information). In general, Ru NPs successfully perform hydrogenation of arene derivatives.[10]

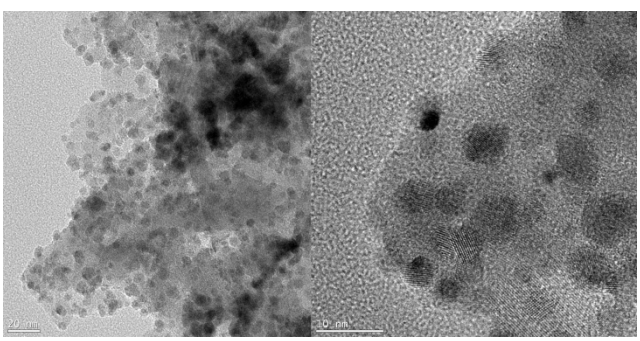
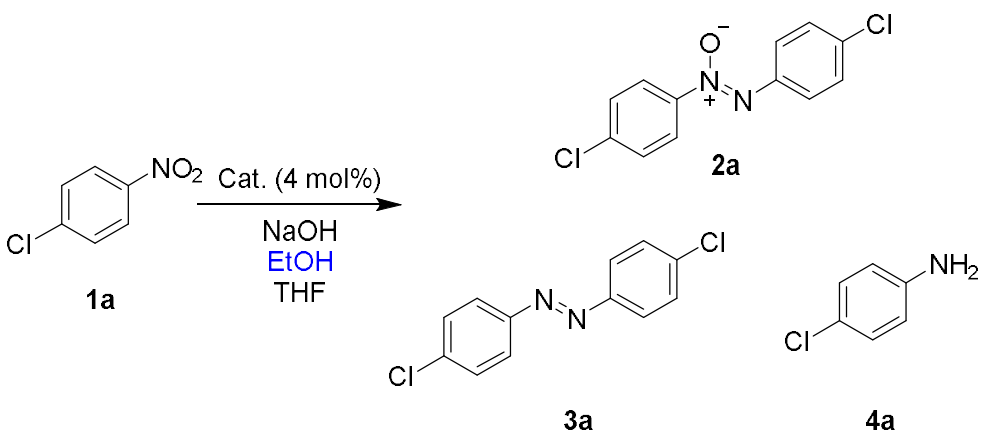


Figure 2.1. High-Resolution TEM images of the catalyst.

At first, we hypothesized that ruthenium nanoparticle is effective for the hydrogenation of nitroarene. Thus, we started a simple reduction chemistry of 4-chloro-1-nitrobenzene in the presence of ethanol. Unexpectedly, unidentified products were obtained through flash column chromatography. After careful analysis of products, we confirmed that the nitrogen-nitrogen dimerized product

was obtained in 41% yield (Table 2.1, entry 1). Furthermore, when the amount of ethanol used was reduced, an azoxy compound was obtained in 46% yield (entry 2). If we could control the chemoselectivity by changing the amount of ethanol used, it would be an unprecedented catalytic reaction to synthesize azobenzene derivatives. Thus, we tried to find optimized reaction conditions for the synthesis of azoxy and azo compounds (Table 2.1).

Table 2.1. Hydrogenation of 4-chloronitrobenzen with optimized conditions[a]



Entry	EtOH (mL)	Temp. (°C)	NaOH (eq.)	Time (h)	Yield[b] (%)		
					2a	**3a**	**4a**
1	0.5	80	1	48		58	41
2[c]	0.3	60	1	48		62	
3[c]	0.3	60	1	40	46		7
4	0.6	80	1	24	65	5	26
5	0.6	60	3	24	33	62	4
6	0.9	60	3	18	31	65	3
7	0.9	60	3	48		83	16
8	0.9	60	4	24		92	5
9	0.2	60	3	24	46		13
10	0.3	60	3	18	88		4
11[d]	0.3	60	3	18	33	60	7
12[e]	-	60	3	18	No reaction		

[a] Reaction conditions: **1a** (1 mmol), 4 mol% of catalyst, 2 mL of THF.
[b] Determined by GC using *o*-xylene as an internal standard. [c] 37~45% of the reactant recovered. [d] Ru/C (activated charcoal) used as a catalyst.
[e] 1 atm (balloon) of H_2 was used

We investigated the reduction of 1-chloro-4-nitrobenzene (**1a**) with ruthenium nanoparticles (Ru NPs) on non-activated charcoal to obtain a maximum yield of aromatic azoxy (**2a**) and azo (**3a**) compounds. In the absence of a base, no reaction was observed for 12 h. Thus, we screened bases such as NaOH, triethylamine (TEA), and *n*-butyl amine. Among them, NaOH was our choice as a base. In the cases of TEA and *n*-butyl amine, small amounts of azo and aniline derivatives were formed. We also screened various alcohols as a hydrogen source. Among them, ethanol was the best choice when we considered the high activity and selectivity (see the Supporting Information, Table S2). The yield of the reaction was highly sensitive to the amounts of ethanol and NaOH. When 0.3 mL of ethanol and 3 equivalents NaOH were used, a high yield (88%) of **2a** was observed (entry 10). Moreover, a high yield (92%) of **3a** was observed in the presence of 0.9 mL of ethanol and 4 equivalents NaOH (entry 9). The use of Ru NPs on activated charcoal showed less selectivity than that of the Ru NPs on non-activated charcoal (entry 11). The formation of **2a** and **3a** was confirmed by ^{1}H NMR and GC-MS.

2.2.2. Substrate Scope

Using the optimum conditions, the synthesis of azoxybenezne derivatives from a variety of nitrobenzenes were examined (Table 2.2). Depending upon the substrate (**1a-1k**), the amount of NaOH used was varied from 3 to 4 equivalents.

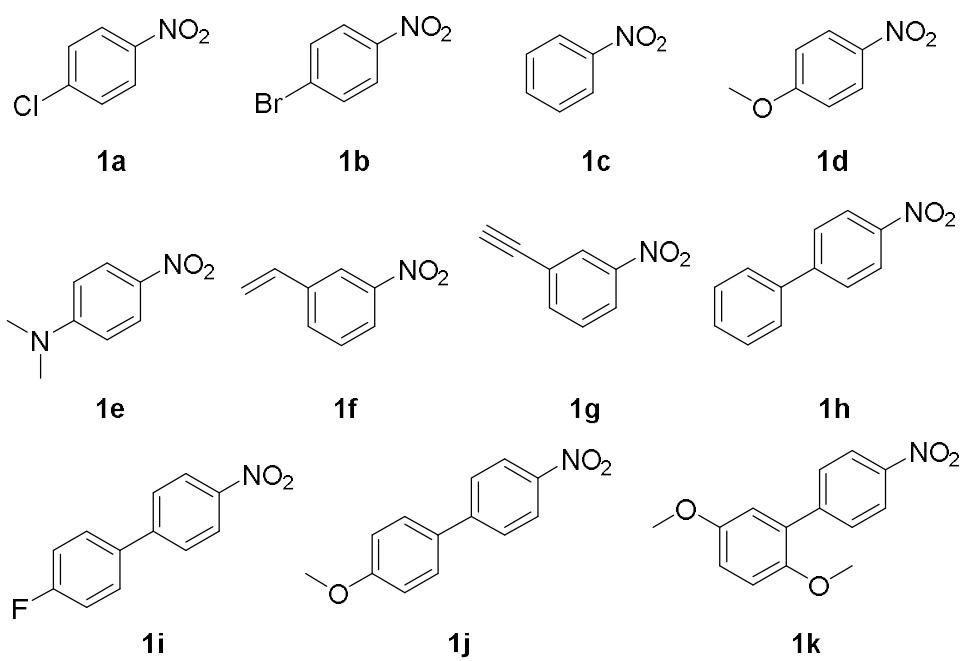
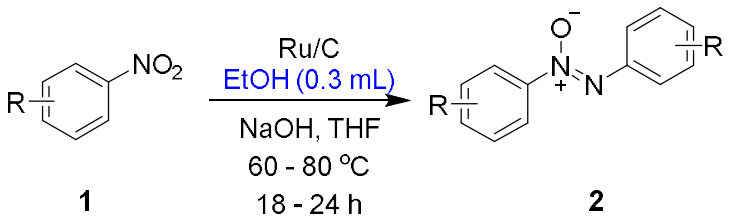


Figure 2.2. Substrate Structures of nitroarene derivatives using Table 2.2–2.4.

Table 2.2. Synthesis of Azoxybenzene[a]



1 **2**

Entry	Substrate	Temp. (°C)	NaOH (eq.)	Time (h)	Yield[b] (%)
1[c]	**1a**	60	3	18	**2a**, 88
2	**1b**	70	3	18	**2b,** 65 (8)
3[c,d]	**1c**	60	3	18	**2c,** 89
4	**1d**	60	4	24	**2d,** 60 (24)
5	**1e**	80	4	24	**2e,** 65 (24)
6	**1f**	70	4	24	**2f,** 63 (20)
7	**1g**	60	3	18	**2g,** 50 (15)
8[d]	**1h**	60	3	40	**2h,** 70 (21)
9[d]	**1i**	60	3	40	**2i,** 73 (15)
10	**1j**	60	4	24	**2j,** 65 (11)
11	**1k**	80	3	18	**2k,** 54 (12)

[a] Reaction conditions: **1** (1 mmol), 4 mol% of catalyst, 4 mL of THF.
[b] Isolated yields. Yields of aniline derivatives were given in parenthesis.
[c] Determined by GC using *o*-xylene as an internal standard.
[d] 2 mL of THF used.

Halogenated nitro compounds (entries 1 and 2) were reduced to the azoxy compounds without losing halides. Nitroarenes containing various electron withdrawing (entries 1 and 2)/donating groups (entries 4 and 5) converted to the corresponding azoxybenzenes in good to high yields. In general, lower yields under harsh reaction conditions were observed with an electron donating group. Sensitive functional groups such as double bond and triple bond (entries 6 and 7) did not undergo any change under the reaction conditions. However, the comparatively lower yields than others might be due to polymerization of the reactants. Biphenyl nitro compounds were also good substrates (entries 8-11). However, higher reaction temperatures were needed presumably due to the solubility problem. The reaction products were extracted and purified by column chromatography with dichloromethane. The structure of the azoxy produced was also confirmed by X–ray diffraction analysis of **2d** (Figure 2.3).

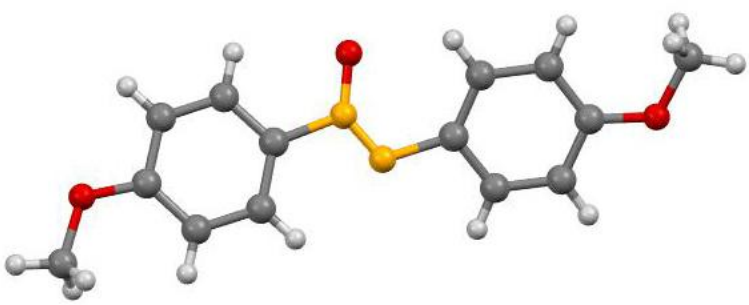
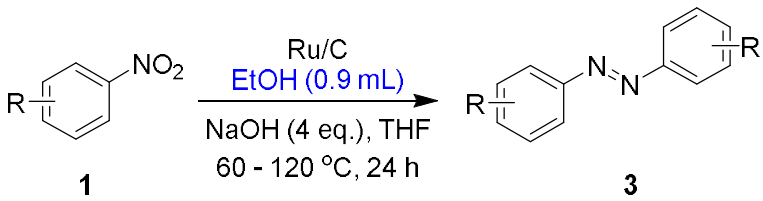


Figure 2.3. X-ray crystal structure of **2d**.

Table 2.3. Synthesis of Azobenzene[a]



1 3

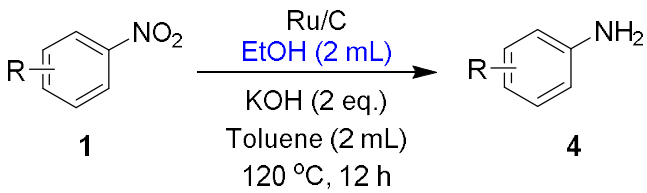
Entry	Substrate	Temp. (°C)	Yield[b] (%)
1[c,d]	**1a**	60	**3a**, 92
2	**1b**	90	**3b,** 52 (16)
3[c,d]	**1c**	100	**3c,** 90
4[e]	**1d**	120	**3d,** 33 (30)
5[e]	**1e**	120	**3e,** 30 (37)
6	**1f**	100	**3f,** 44 (22)
7	**1g**	100	**3g,** 37 (14)
8[d]	**1h**	105	**3h,** 65 (22)
9[d]	**1i**	105	**3i,** 70 (20)
10[f]	**1j**	60	**3j**
11	**1k**	110	**3k,** 56 (8)

[a] Reaction conditions: **1** (1 mmol), 4 mol% of catalyst, 4 mL of THF.
[b] Isolated yields. Yields of aniline derivatives were given in parenthesis.
[c] Determined by GC using *o*-xylene as an internal standard.
[d] 2 mL of THF used. [e] From azoxy derivatives. [f] No azo compound observed

Aromatic azo compounds were directly obtained from nitroarenes by reduction with ethanol in the presence of the Ru NPs on non-activated charcoal (Table 2.3). Compared to the synthesis of azoxy compounds, relatively higher temperatures (60 – 120 ^{o}C) and longer reaction times (24 h) were required. Due to the high reaction temperatures, nitroarene derivatives bearing an electron-donating group (entries 4, 5, and 10) or a reducible functional group (entries 6 and 7) afforded rather low yields. In the cases of entries 4 and 5, the yields were based on the two-step, one-pot, one-catalyst reaction, i.e., the substrate was reacted with the Ru NPs on non-activated charcoal in the presence of 0.3 mL of C_2H_5OH at 60^{o}C, then 0.9 mL C_2H_5OH was added and the resulting solution was heated at 120^{o}C. For the substrates in entries 6 and 7, the yields were poor presumably due to the polymerization. However, the preferential reduction of a nitro group in the presence of double and triple bonds was observed. Strangely, in the case of entry 10, an aniline derivative was observed instead of an azo compound. The structure of the azobenzene produced was confirmed by an X–ray diffraction study of **3k** (see Fig. S1).

We next examined the reduction of aromatic nitrobenzene to anilines (Table 2.4). Functionalized nitroarenes except 1-methoxy-4-nitrobenzene (entry 4) and 1-ethynyl-3-nitrobenzene (entry 7) were converted to the corresponding substituted anilines in high yields with the other functional groups remaining intact. For 1-methoxy-4-nitrobenzene, 4-methoxy- and 4-ethoxyaniline were formed in 70% and 30% yields, respectively. In the case of 1-ethynyl-3-nitrobenzene, a considerable amount of polymeric materials were formed. There have been few reports on the reduction of 1-ethynyl-3-nitrobenzene. However, the preferential reduction of a nitro group in the presence of C=C and C≡C bonds was still observed under our reaction conditions.[11]

Table 2.4. Synthesis of Aromatic Amines



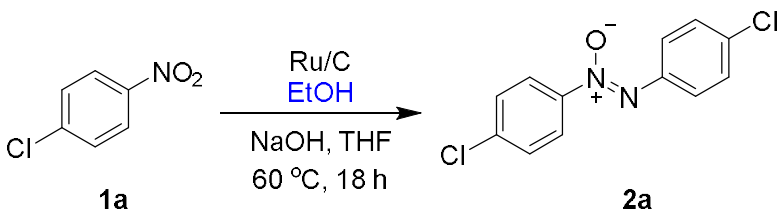
Entry	Substrate	Cat. (mol %)	Yield[a] (%)
1	**1a**	8	**4a**, 99
2	**1b**	8	**4b,** 92
3	**1c**	12	**4c,** 99
4	**1d**	12	**4d,** 70 (30)[b]
5	**1e**	12	**4e,** 73[c]
6	**1f**	8	**4f,** 85
7	**1g**	8	**4g,** 16
8	**1h**	12	**4h,** 99 (84)[c]
9	**1i**	8	**4i,** 75[c]
10	**1j**	12	**4j,** 65[c]
11	**1k**	12	**4k,** 83[c]

[a] Determined by GC using *o*-xylene as an internal standard.
[b] 4-ethoxy aniline was formed. [c] Isolated yields

2.2.3. Reusability and Mechanistic Investigation

The reusability of the catalyst was also tested in the reduction of nitrobenezene to azoxybenzene (Table 2.5). After completion of reaction, the catalyst was separated from the reaction mixture by centrifugation, washed with dichloromethane, water and acetone and dried *in vaccuo*. The recovered catalyst was reused in the next runs under the same conditions. The results indicate that there is no appreciable difference in the yields of the product even after a 5th run.

Table 2.5. Synthesis of Aromatic Amines[a]

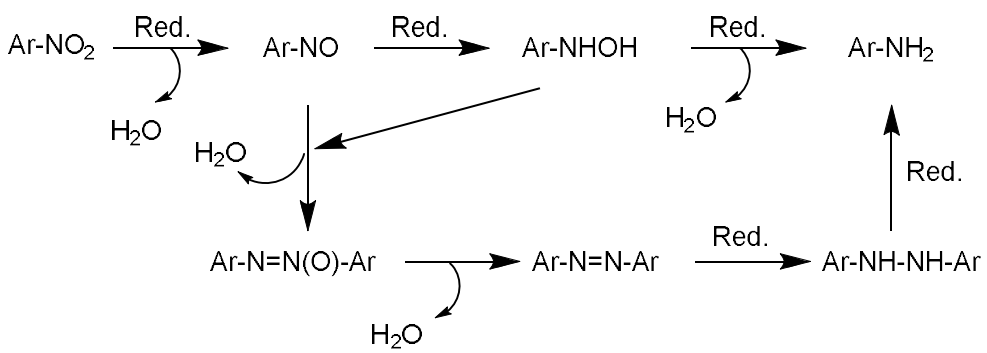


1a **2a**

Entry	Catalyst	Yield of **2a**[b] (%)
1	1st run	**88 (10)**
2	2nd run	**85 (9)**
3	3rd run	**83 (10)**
4	4th run	**83 (9)**
5	5th run	**83 (9)**

[a] Reaction conditions: **1a** (1 mmol), 4 mol% of catalyst, 0.3 mL of EtOH, 2 mL of THF, 60 °C, and 18 h.
[b] Determined by GC using o-xylene as an internal standard. Yields of aniline derivatives were given in parenthesis.

Although the exact mechanism for the reduction is not clear, we think that it is similar to that of other heterogeneous catalysts.[12] A plausible reaction mechanism is proposed in Scheme 2.3. In terms of the mechanism of reduction, one might envisage that the present Ru NPs-catalyzed reaction could proceed by the reduction of nitro compounds with hydrogen gas generated in situ from ethanol. However, this possibility can be eliminated, as there was virtually no reaction when H_2 was used instead of ethanol as the reducing agent (Table 2.1, entry 12). It seems that the catalytic reduction is initiated by coordinating the nitro group of the substrate and the hydroxyl group of the alcohol on the surface of nanoparticles at Lewis acidic sites. The alcohol molecule can be easily converted to alkoxide species in the presence of a NaOH (or KOH) base, which is well known as an activated H-donor. The adsorbed nitro group of the substrate is attacked by the metal-hydride, leading to a direct hydride transfer from the alcohol to adjacent substrate molecules. The formation of aniline from nitrobenzene proceeds via the formation of nitrosobenzene and N-phenylhydroxylamine as the intermediates. Moreover, the condensation of one molecule of nitrosobenzene with a molecule of N-phenylhydroxylamine leads to the azoxy compound, which is reduced in a series of consecutive steps to the azobenzene and aromatic amine compounds.



Scheme 2.3. Constructing azo, azoxy and amine compound with Ruthenium nanoparticle catalytic system of nitroarenes

2.3. Conclusion

In this chapter, we have developed a catalytic system that can produce an azo, an azoxy, or an amine as a major product just by changing the reaction conditions. This novel methodology is highly chemoselective, tolerating a large range of functional groups such as halo, double and triple bonds. The high chemoselectivity of the catalytic system might be due to the slowness of the reaction in the presence of Ru nanoparticles. Some remarkable advantages of this catalytic system include the use of ethanol as a sustainable source of hydrogen and the reusability of the catalyst and the stability of the Ru NPs on non-activated charcoal toward air and moisture, allowing the reaction to be carried out under atmospheric conditions. All these features make this method an attractive and useful alternative in organic synthesis.

2.4. Experimental Section

Materials

All solvents were dried and distilled according to standard methods before use. Solvents utilized in this work were obtained from Fisher Scientific (tetrahydrofuran and ethanol- HPLC grade), Sigma-Aldrich (toluene- ACS grade), and Samchun Pure Chemicals (hexanes, ethyl acetate, dichloromethane and acetone). Tetrahydrofuran (THF) and toluene were dried over Na/benzophenone and subsequently distilled from these reagents under nitrogen. n-hexanes and ethyl acetate were used without further purification. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, TCI, or Strem and were used as received. Ruthenium on activated charcoal was purchased from Sigma-Aldrich. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254). The TLC plate was visualized by UV-light (254 nm) and treatment with acidic *p*-anisaldehyde and $KMnO_4$ stain followed by gentle heating. Workup procedures were done in air. Flash column chromatography was carried out on Merck 60 silica gel (230 – 400 mesh).

Characterization

^{1}H and ^{13}C NMR spectra were recorded with Bruker (300 MHz and 75 MHz, respectively) spectrometer. ^{1}H NMR spectra were taken in $CDCl_3$ and were referenced to residual TMS (0 ppm) and reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.00 ppm). Mass spectral data were obtained at the Korea Basic Science Institute (Daegu) on a Jeol JMS 700 high resolution mass spectrometer. GC-MS analyses were performed with a HP-6890 series with a HP-5 capillary column (30 m x 0.25 mm; coating thickness 0.25 μm) and Agilent 5973 Network Mass

Selective detector. The amount of the Ru loading was measured by Inductively coupled plasma atomic emission spectroscopy (ICP-AES) with OPTIMA 4300DV, Perkin-Elmer (Argon Plasma, 6000 K). The nanoparticles were characterized by high-resolution transmission electron microscopy (HRTEM) at the National Nanofab Center in Daejeon, South Korea and the Energy-dispersive X-ray spectroscopy (EDS) was also obtained at the National Nanofab Center using an iXRF EDS 2011 system 126eV. FTIR were performed with a Nicolet iS10 FT-IR Spectrometer (ThermoFisher Scientific). Single crystal data for **2d** and **3k** were collected on an Enraf-Nonius CCD single crystal X-ray diffractometer at room temperature using graphite-monochromated MoK α radiation (λ= 0.71073Å). Structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares with SHELXL-97. **2a**,[8b] **2c**, [8b] **3a**, [8b] **3c**, [8b] **4c**,[13] **4g**,[14] were known compounds.

Synthesis

Immobilization of Ruthenium Nanoparticle on non-activated charcoal[9a]

To a two-neck flask were added $RuCl_3 \cdot 3H_2O$ (0.5 g), ethylene glycol (15 mL), and flame-dried charcoal (1.0 g). After the solution was heated at 180 ^oC for 10 min, the reaction mixture was cooled to room temperature. Most of the ethylene glycol was removed by washing with 0.3 M $NaNO_3$ aqueous solution. The solid phase was collected by filtration and washed with diethyl ether (20 mL), dichloromethane (20 mL), acetone (20 mL), and ethanol (20 mL). Vacuum drying gave a black solid.

Procedure for the synthesis of 1,2-bisarenediazene oxide from nitrobenzene derivatives (2)

Reactions were performed in a microwave tube equipped with a stirring bar and capped with an aluminum cap and the followings were placed in the tube in order: 1 mmol of **1**, 3 ~ 4 equiv of NaOH, 4 mol % of catalyst (25 mg of the immobilized Ru nanoparticle on non-activated charcoal), 0.3 mL of ethanol, 60 μL of *o*-xylene (as an internal standard), and 4 mL of THF. The mixture was stirred at 60 ~ 80 ^{o}C for 18 ~ 24 h. The reaction mixture was extracted with aqueous NH_4Cl solution and ethyl acetate or dichloromethane. The mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 10:1) to afford **2**

2b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (t, *J* = 9.6 Hz, 4 H), 8.07 (d, *J* = 8.5 Hz, 2 H) 8.16 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.5, 123.8, 126.4, 127.2, 131.9, 132.0, 132.3, 142.5; HRMS (EI) calc. for $[C_{12}H_8Br_2N_2O]^+$ 355.9003, found 355.8985; m.p. 167 ^{o}C

2d: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3 H), 3.88 (s, 3 H), 6.97 (dd, *J* = 5.2, 9.0 Hz, 4 H), 8.26 (t, *J* = 9.6 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 55.6, 113.5, 113.6, 123.7, 127.7, 137.9, 141.6, 160.1, 161.7; HRMS (EI) calc. for $[C_{14}H_{14}N_2O_3]^+$ 258.1004, found 258.1001; m.p. 115 ^{o}C

2e: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.04 (s, 6 H), 3.05 (s, 6 H), 6.67 (d, *J* = 9.3 Hz, 2 H), 6.72 (d, *J* = 9.3 Hz, 2 H), 8.16 (d, *J* = 9.3 Hz, 2 H), 8.29 (d, *J* = 9.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.2, 40.3, 110.7, 111.0, 123.1, 126.0, 127.8, 134.6, 150.4, 151.6; HRMS (EI) calc. for $[C_{16}H_{20}N_4O]^+$ 284.1637, found 284.1637; m.p. 242 ^{o}C

2f: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.32 (d, *J* = 10.9 Hz, 1 H), 5.39 (d, *J* = 10.9 Hz, 1 H), 5.86 (t, *J* = 17.4 Hz, 2 H), 6.78 (ddd, *J* = 5.7, 10.9, 17.0 Hz, 2 H), 7.45 (m, 3 H), 7.58 (m, 1 H), 8.08 (dd, *J* = 3.2Hz, 5.8Hz, 1 H,), 8.18 (m, 2 H), 8.33 (d, *J* = 1.6Hz, 1 H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 114.8, 115.9, 119.9, 121.4, 123.4,

124.6, 127.3, 128.8, 128.9, 129.2, 135.5, 136.2, 138.1, 138.6, 144.2; HRMS (EI) calc. for $[C_{16}H_{14}N_2O]^+$ 250.1106, found 250.1102; m.p. 36 °C

2g: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.12 (s, 1 H), 3.18 (s, 1 H), 7.47 (m, 4 H), 7.67 (d, *J* = 7.3 Hz, 1 H), 8.14 (d, *J* = 7.6 Hz, 1 H), 8.28 (m, 2 H), 8.42 (s, 1 H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.8, 78.8, 82.0, 82.8, 122.6, 122.7, 123.1, 125.9, 126.0, 128.7, 128.9, 129.1, 133.1, 135.1, 143.6, 148.0; HRMS (EI) calc. for $[C_{16}H_{10}N_2O]^+$ 246.0793, found 246.0791; m.p. 100 °C

2h: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (m, 6 H), 7.68 (m, 8 H), 8.32 (d, *J* = 8.4 Hz, 2 H), 8.39 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.8, 126.2, 127.0, 127.2, 127.3, 127.8, 128.2, 128.8, 128.9, 139.5, 140.1, 142.2, 143.2, 144.4, 147.3; HRMS (EI) calc. for $[C_{24}H_{18}N_2O]^+$ 350.1419, found 350.1416; m.p. 201 °C

2i: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (m, 4 H), 7.64 (m, 8 H), 8.31 (d, *J* = 8.5 Hz, 2 H), 8.39 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.7, 115.8, 116.0, 116.1, 122.9, 126.3, 127.1, 127.3, 128.7, 128.8, 128.9, 129.0, 141.3, 143.2, 143.5; HRMS (EI) calc. for $[C_{24}H_{16}F_2N_2O]^+$ 386.1231, found 386.1228.

2j: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (d, *J* = 1.2 Hz, 6 H), 7.02 (dd, *J* = 3.9, 8.6 Hz, 4 H), 7.61 (dd, *J* = 6.1, 8.4 Hz, 4 H), 7.69 (d, *J* = 7.3 Hz, 4 H), 8.31 (d, *J* = 8.6 Hz, 2 H), 8.37 (d, *J* = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4, 114.3, 114.4, 122.7, 126.2, 126.6, 126.8, 128.1, 128.3, 132.6, 139.8, 141.8, 142.7, 146.8, 159.6, 159.8; IR (cm^{-1}): 2928, 1597, 1517, 1488, 1456, 1342, 1253, 1185, 1037, 910, 845, 825; HRMS (EI) calc. for $[C_{26}H_{22}N_2O_3]^+$ 410.1630, found 410.1631; m.p. 230 °C

2k: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 6 H), 3.82 (m, 6 H), 6.92 (m, 6 H), 7.68 (d, *J* = 8.0 Hz, 4 H), 8.27 (d, *J* = 8.1 Hz, 4 H), 8.35 (d, *J* = 8.1 Hz, 4 H); ^{13}C NMR

(75 MHz, $CDCl_3$): δ 55.8, 56.2, 56.3, 56.4, 112.4, 112.7, 112.8, 113.5, 116.4, 116.5, 121.9, 125.3, 129.6, 129.8, 129.9, 130.6, 139.7, 141.8, 147.0, 150.7, 150.8, 153.7; IR (cm^{-1}): 2990, 2960, 2830, 1594, 1506, 1486, 1453, 1320, 1106, 1019, 915, 867, 741; HRMS (EI) calc. for $[C_{28}H_{26}N_2O_5]^+$ 470.1842, found 470.1844; m.p. 142 °C

Procedure for the synthesis of 1,2-bisaryldiazene from nitrobenzene derivatives (3)

Reactions were performed in a microwave tube equipped with a stirring bar and capped with a aluminum cap. The followings were placed in the tube in order: 1 mmol of **1**, 4 equiv of NaOH (0.16 g, 4 mmol), 4 mol % of catalyst (25 mg of the immobilized Ru nanoparticle on non-activated charcoal), 0.9 mL of ethanol, 60 μL of *o*-xylene (as an internal standard), and 4 mL of THF. The mixture was stirred at 60 – 120 °C for 24 h. The reaction mixture was extracted with aqueous NH_4Cl solution and ethyl acetate or dichloromethane. The mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 10:1) to afford **3**

3b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.6 Hz, 4 H), 7.80 (d, J = 8.5 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 124.4, 125.7 132.3, 151.1; HRMS (EI) calc. for $[C_{12}H_8Br_2N_2]^+$ 337.9054, found 337.9054; m.p. 190 °C

3d: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 6 H), 7.00 (d, J = 8.9 Hz, 4 H), 7.88 (d, J = 8.9 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 114.1, 124.3, 147.0, 161.5; HRMS (EI) calc. for $[C_{14}H_{14}N_2O]^+$ 242.1055, found 242.1052; m.p. 148 °C

3e: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.05 (s, 12 H), 6.76 (d, J = 9.2 Hz, 4 H), 7.81 (d, J = 9.2 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.4, 111.7, 123.9, 144.1, 151.4; HRMS (EI) calc. for $[C_{16}H_{20}N_4]^+$ 268.1688, found 268.1689; m.p. 260 °C

3f: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.35 (d, *J* = 10.9 Hz, 2 H), 5.88 (d, *J* = 17.6 Hz, 2 H), 6.81 (dd, *J* = 10.9, 17.5 Hz, 2 H), 7.49 (m, 4 H), 7.82 (d, *J* = 7.3 Hz, 2 H), 7.97 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.0, 120.5, 122.1, 128.7, 129.2, 136.1, 138.5, 152.8; HRMS (EI) calc. for $[C_{16}H_{14}N_2]^+$ 234.1157, found 234.1159; m.p. 76 °C

3g: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15 (s, 2 H), 7.47 (t, *J* = 7.8 Hz, 2 H), 7.60 (d, *J* = 7.6 Hz, 2 H), 7.90 (d, *J* = 7.9 Hz, 2 H), 8.04 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 78.1, 82.8, 123.1, 123.6, 126.3, 129.1, 134.5, 152.1; HRMS (EI) calc. for $[C_{16}H_{10}N_2]^+$ 230.0844, found 230.0845; m.p. 126 °C

3h: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (m, 6 H), 7.68 (d, *J* = 7.2 Hz, 4 H), 7.77 (d, *J* = 8.1 Hz, 4 H), 8.03 (d, *J* = 8.0 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.3, 127.1, 127.7, 127.8, 128.9, 140.1, 143.7, 151.8; HRMS (EI) calc. for $[C_{24}H_{18}N_2]^+$ 334.1470, found 334.1472; m.p. 254 °C

3i: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (t, *J* = 8.6 Hz, 4 H), 7.64 (dd, *J* = 5.4, 8.6 Hz, 4 H), 7.71 (d, *J* = 8.4 Hz, 4 H), 8.02 (d, *J* = 8.4 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.7, 115.9, 123.4, 127.6, 128.7, 128.8, 142.7, 151.8; IR (cm^{-1}): 3070, 2923, 2853, 1594, 1519, 1485, 1396, 1246, 1168, 825, 742; HRMS (EI) calc. for $[C_{24}H_{16}F_2N_2]^+$ 370.1282, found 370.1281; m.p. 239 °C

3k: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 6 H), 3.82 (s, 6 H), 6.93 (m, 6 H), 7.70 (d, *J* = 8.6 Hz, 4 H), 7.98 (d, *J* = 8.6 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 56.3, 112.8, 113.6, 116.5, 122.5, 130.1, 130.7, 141.1, 150.8, 151.5, 153.7; IR (cm^{-1}): 3087, 3041, 3003, 2949, 2831, 1584, 1503, 1488, 1452, 1296, 1257, 1149, 1050, 825, 736; HRMS (EI) calc. for $[C_{28}H_{26}N_2O_4]^+$ 454.1893, found 454.1890; m.p. 170 °C

Procedure for the synthesis of aniline derivatives from nitrobenzene derivatives (4)

Reactions were performed in a microwave tube equipped with a stirring bar and capped with a aluminum cap and the followings were placed in the tube in order: 1 mmol of **1a**, 2 equiv of KOH (0.11 g, 2 mmol), 8- 12 mol % of catalyst, 2 mL of ethanol, 60 μL of *o*-xylene (as an internal standard), and 2 mL of toluene. The mixture was stirred at 120 ^{o}C for 12 h. The reaction mixture was extracted with aqueous NH_4Cl solution and ethyl acetate. The mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 5:1) to afford **4**

4a: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64 (s, 2 H), 6.60 (d, J = 8.6 Hz, 2 H), 7.10 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.2, 129.1, 134.3, 144.9; HRMS (EI) calc. for $[C_6H_6ClN]^+$ 127.0189, found 127.0187.

4b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 2 H), 6.56 (d, J = 8.2 Hz, 2 H), 7.23 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.2, 116.7, 132.0, 145.4; HRMS (EI) calc. for $[C_6H_6BrN]^+$ 170.9684, found 170.9686.

4d + 4-ethoxyaniline: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 3.42 (br s, 2 H, NH_2), 3.73 (s, 3 H, OCH_3), 3.95 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 6.63 (m, 3 H), 6.74 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.9 (OCH_2CH_3), 55.6 (OCH_3), 63.9 (OCH_2CH_3), 114.7, 115.6, 116.3, 139.9, 152.0, 152.7; HRMS (EI) calc. for $[C_7H_9NO]^+$ (methoxy) 123.0684, found 123.0686. calc. for $[C_8H_{11}NO]^+$ (ethoxy) 137.0841, found 137.0842.

4e: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81 (s, 6 H), 3.32 (s, 2 H), 6.67 (q, J = 8.4 Hz, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.0, 115.5, 116.5, 137.8, 144.7; HRMS (EI) calc. for $[C_8H_{12}N_2]^+$ 136.1000, found 136.1000.

4f: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (s, 2 H), 5.19 (dd, *J* = 0.8, 10.8 Hz, 1 H), 5.69 (dd, *J* = 0.9, 17.6 Hz, 1 H), 6.60 (m, 2 H), 6.71 (m, 1 H), 6.81 (d, *J* = 7.6 Hz, 1 H), 7.10 (t, *J* = 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.6, 113.6, 114.7, 116.8, 129.4, 136.9, 138.6, 146.5; HRMS (EI) calc. for $[C_8H_9N]^+$ 119.0735, found 119.0736.

4h: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 2 H), 6.74 (d, *J* = 8.4 Hz, 2 H), 7.25 (m, 1 H), 7.39 (m, 4 H), 7.53 (d, *J* = 7.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.3, 126.2, 126.3, 128.0, 128.6, 131.5, 141.1, 145.8; HRMS (EI) calc. for $[C_{12}H_{11}N]^+$ 169.0891, found 169.0890.

4i: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 2 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 7.05 (t, *J* = 8.7 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.44 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.2, 115.3, 115.5, 127.7, 127.8, 130.4, 137.2, 145.8, 160.1, 163.4; HRMS (EI) calc. for $[C_{12}H_{10}FN]^+$ 187.0797, found 187.0797.

4j: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 2 H), 3.81 (s, 3 H), 6.72 (d, *J* = 8.2 Hz, 2 H), 6.93 (d, *J* = 8.5 Hz, 2 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.3, 114.0, 115.4, 127.3, 127.5, 131.2, 133.8, 145.3, 158.3; HRMS (EI) calc. for $[C_{13}H_{13}NO]^+$ 199.0997, found 199.1000.

4k: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.65 (s, 2 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 6.65 (m, 2 H), 6.81 (m, 3 H), 7.33 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 56.1, 111.9, 112.5, 114.5, 116.1, 128.1, 130.1, 131.6, 145.5, 150.6, 153.5; HRMS (EI) calc. for $[C_{14}H_{15}NO_2]^+$ 229.1103, found 229.1104.

2.5. Supporting Information

Characterization of Catalyst and Screening various alcohols as a hydrogen source

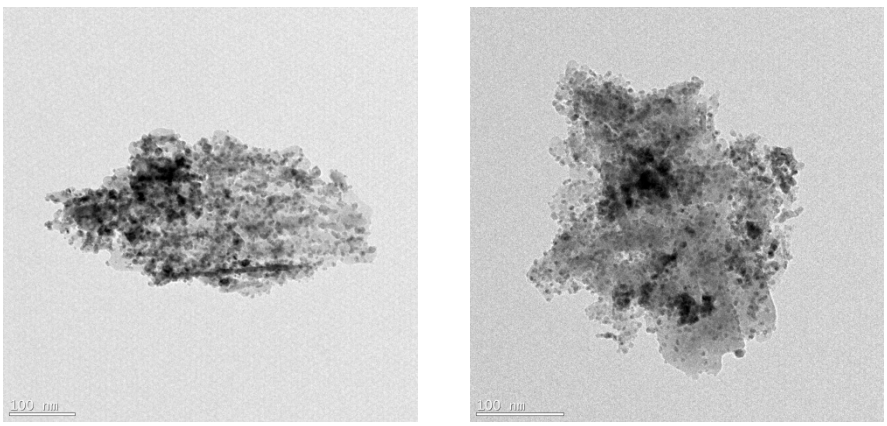


Figure S2.1. HRTEM images of Ru NPs on nonactivated charcoal (100 nm)

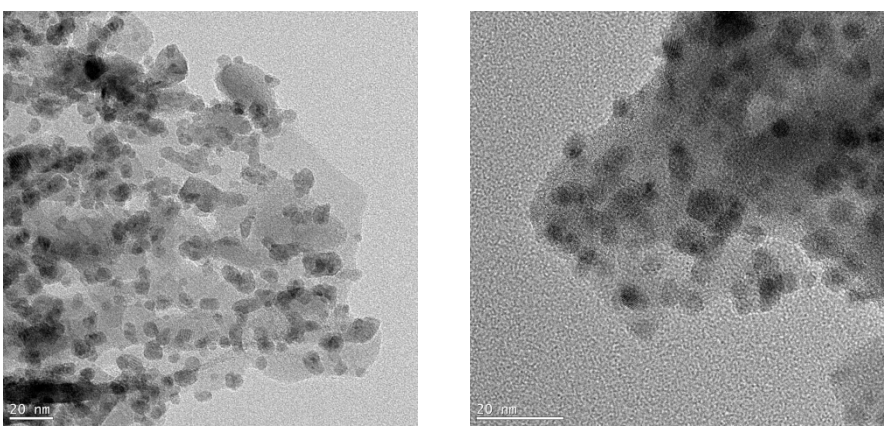


Figure S2.2. HRTEM images of Ru NPs on nonactivated charcoal (20 nm)

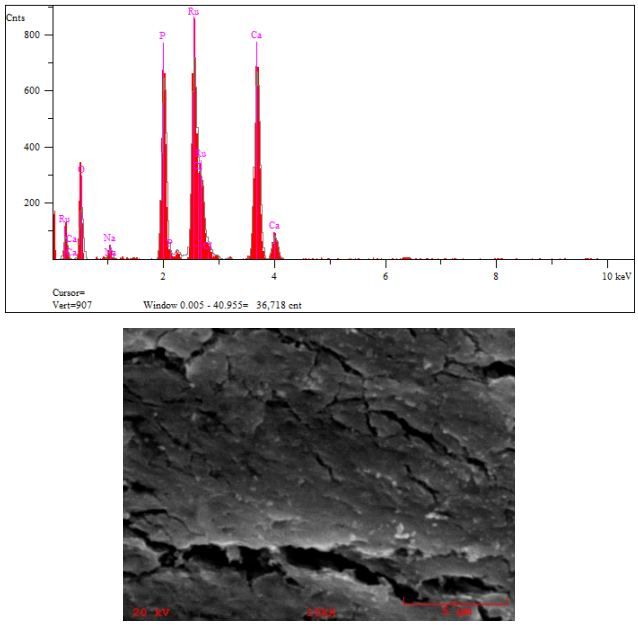


Figure S2.3. EDS spectrum of Ru NPs on nonactivated charcoal

Elt.	Line	Atomic %	Conc	Units	
O	Ka	46.948	20.183	wt.%	
Na	Ka	2.327	1.437	wt.%	
P	Ka	14.446	12.023	wt.%	
Cl	Ka	0.480	0.457	wt.%	
Ca	Ka	19.112	20.581	wt.%	
Ru	La	16.687	45.319	wt.%	
		100.000	100.000	wt.%	Total

Table S2.1. Weight and atomic percent content of Ru NPs on nonactivated charcoal

Because of using non-activated charcoal, other elements such as Na, P, and Ca were detected.

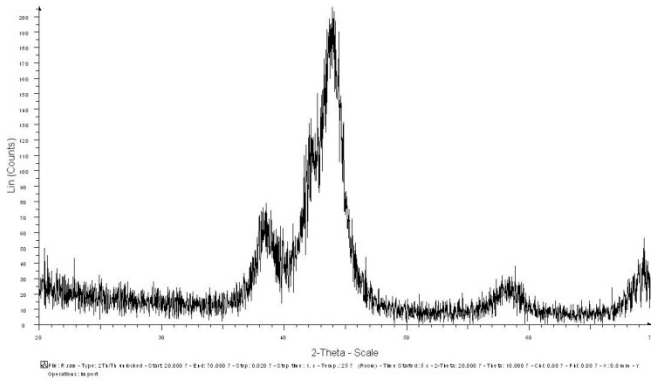


Fig S2.4. XRD of NPs on non-activated charcoal [9a, 15]

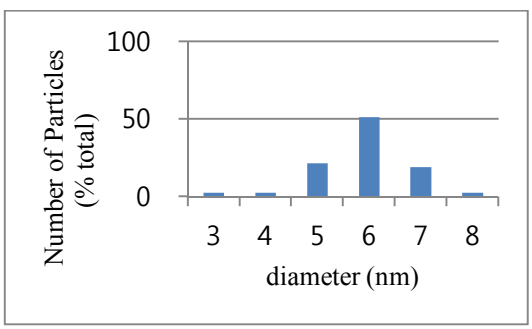
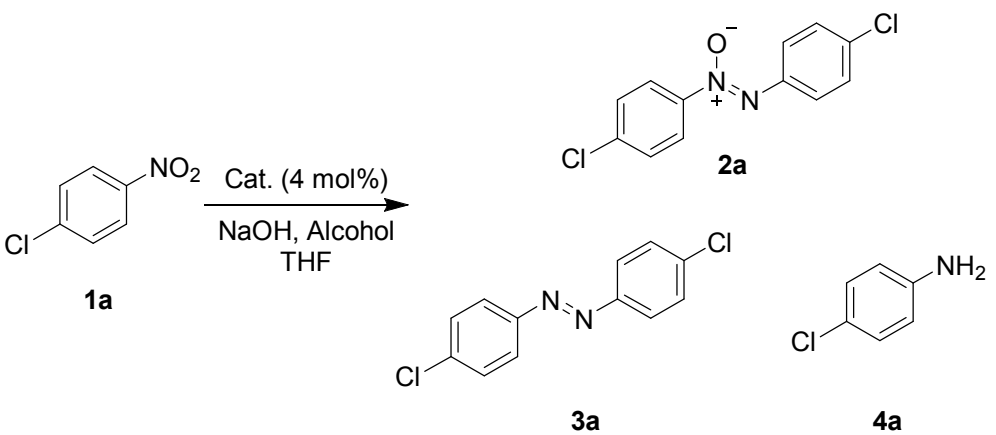


Fig S2.5. Size distribution of Ru NPs on nonactivated charcoal as determined from HRTEM

Table S2.2. Screening various alcohols as a hydrogen source



Entry	Alcohols	Yield[b] (%)		
		2a	**3a**	**4a**
1[c]	Methanol	52		
2	Ethanol	88		
3	Isopropyl alcohol	24		31
4	*sec*-phenethyl alcohol	23		22
5	Allyl alcohol		34	28
6	*n*-heptanol	40	14	22
7	Cinnamyl alcohol		53	15

[a] Reaction conditions: **1a** (1 mmol), 4 mol% of catalyst, 0.3 mL of alcohol, 60 °C, 18 h, 2 mL of THF.
[b] Determined by GC using o-xylene as an internal standard.
[c] 1-methoxy-4-nitrobenzene was obtained. (45 % yield)

2.6. References

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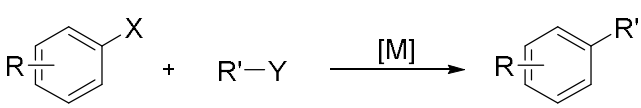
Chapter 3. Copper Nanoparticle-Catalyzed Cross-Coupling of Alkyl Halides with Grignard Reagents

3.1. Introduction

As described in Chapter 2, we developed the ruthenium nanoparticle-catalyzed hydrogenation and dimerization of nitroarene derivatives. To expand the scope of catalytic reaction using nanoparticle catalysts, we studied the cross-coupling reactions. Transition metal-catalyzed cross-coupling reactions between two different partners, e.g., an organometallic reagent and an electrophile, have been developed as an arsenal for the formation of carbon–carbon bonds in organic synthesis.[1] Thus, a variety of electrophilic coupling partners, aryl, vinyl, and alkynyl halides, and pseudo-halides, can be readily coupled (Scheme 3.1). However, the coupling of non-activated alkyl halides, especially having tertiary alkyl carbon, remain difficult due to steric hindrance, chance to β–hydride elimination, and isomerization of alkylmetals.[2]



X = MgBr, Zn, Sn, $B(OR'')_2$, etc.

Y = halides

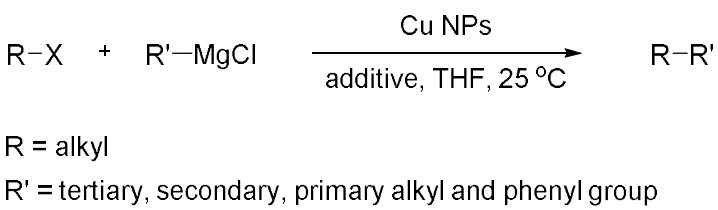
R' = aryl, vinyl, alkynyl, etc.

Scheme 3.1. Transition metal-catalyzed cross-coupling reactions

Since the pioneering work in 1972 by Kumada[3a,3b] and Corriu[3c], there has been rapid development in the use of transition-metal catalysts for a variety of alkyl-alkyl bond formation reactions using Grignard reagents.[4] In particular, copper- and

nickel-based catalytic systems are unparalleled as catalysts.[5-12] In 2013, the cobalt-catalyzed cross-coupling of alkyl halides with secondary and tertiary alkyl Grignard reagents and the copolymer-incarcerated nickel nanoparticle (NP)-catalyzed Kumada reactions were reported.[13,14]

We observed that the chemistry of metal NPs matches the characteristics of the homogeneous metal complexes in many cases.[15] However, we found that reports on the transition metal NP-catalyzed cross-coupling reactions of alkyl halides with Grignard reagents are quite rare.[14] Inspired by previous reports[9-11,16,17] on the homogeneous copper-catalyzed cross-coupling reactions, we decided to explore the use of Cu NPs in the cross-coupling reaction of electrophiles with Grignard reagents and found that Cu NPs in the presence of an additive were quite effective catalysts in the cross-coupling reaction of alkyl bromides and chlorides with primary-, secondary-, tertiary-alkyl, or phenyl Grignard reagents under mild conditions (Scheme 3.2).



Scheme 3.2. Copper nanoparticle-catalyzed carbon-carbon bond forming reactions

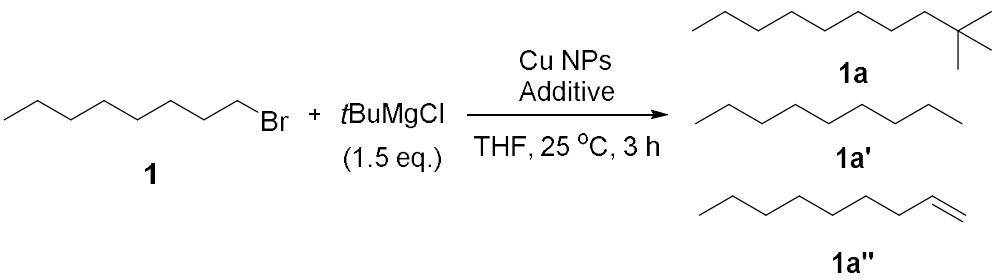
The Cu NPs used in this study are commercially available and reused five times without any loss of activity. The catalytic system doesn't need any pretreatment before use. Moreover, broad substrate scopes such as functionalized alkyl chloride are acceptable and high functional group tolerance could be realized our catalytic system. Thus, we have developed a more convenient methodology with respect to environmental and economic considerations in this study. Chapter 3 will discuss about copper nanoparticle catalyzed carbon-carbon bond forming reaction.

3.2. Results and Discussion

3.2.1. Optimization of reaction conditions and Substrate Scope

Initially, the reaction conditions were adopted from the reaction of carbon-carbon bond forming reaction in the copper-catalyzed reaction.[11,12] Using 1-bromooctane as a model compound, we optimized the reaction with *t*-BuMgCl (Table 3.1). Without a catalyst, no coupling product was formed. In the presence of Cu NPs, which is commercially available, and an alkyne additive, the cross-coupli ng reactions went to completion. The alkyne additive was previously used in the copper-catalyzed cross-coupling reaction with primary alkyl halides.[9] The reaction was highly dependent upon the size of the catalyst and the presence of the additive. We examined three different sizes (5-7 nm, 25-40 nm, and 40-60 n m) of copper NPs and four different alkynes as an additive. The reaction ti me was highly dependent upon the alkyl halide. For example, the reaction o f 5-bromo-1-pentanol with *t*-BuMgCl went to completion within 10 min. For the convenience of experimental manipulation, the cross-coupling reactions w ere carried out under the following reaction conditions: 1.0 mmol of a substrate, 10 mol% of Cu NPs,[18] 20 mol% of 1-phenylpropyne, 1 mL of TH F, 25 ^{o}C, and 3 h of a reaction time. Interestingly, a catalytic reaction under went in the presence of copper (II) oxide NPs. However, the reactivity of copp er (II) oxide NPs was slight lower than that of copper NPs. Other copper sources, such as metallic copper powder and copper oxide powder, gave no product.

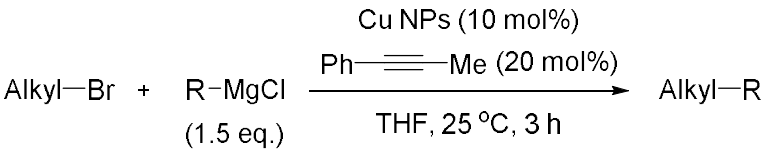
Table 3.1. Screening the size of the Cu NPs catalyst and additives[a]

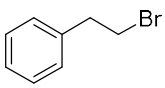
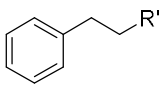
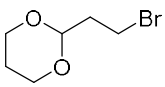
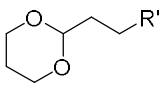
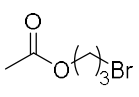
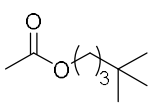
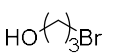
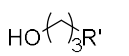
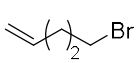
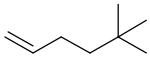
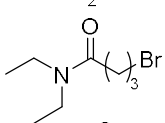
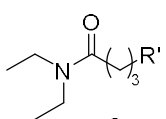
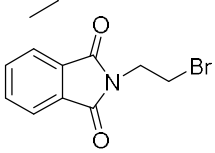
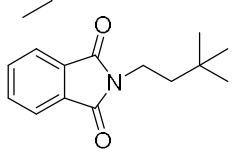
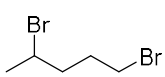
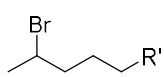


Entry	Cat. size (nm)	Types of Additive	Amounts of Additive (mol %)	Yield[b] (%)		
				1a	1a'	1a''
1	25-40	Ph—≡—Me	20	>99		
2	40-60	Ph—≡—Me	20	>99		
3	5-7	Ph—≡—Me	20	41	13	23
4	25-40	Ph—≡—Et	20	>99		
5	25-40	Ph—≡—Ph	20	>99		
6[c]	25-40	Ph—≡—H	20	72		
7	25-40	Ph—≡—Me	40	>99		
8	25-40	Ph—≡—Me	80	>99		

[a] Reaction conditions: **1** (1 mmol), 10 mol% of catalyst, 1 mL of THF.
[b] Determined by GC using 1,3,5-trimethyl benzene as an internal standard.
[c] 27 % of reactant was recovered.

Table 3.2. Cu NP-catalyzed cross-coupling reactions of alkyl bromides with various Grignard reagents[a]

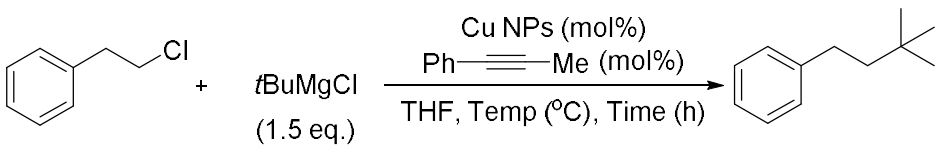


Entry	Substrate	Product	R	Yield[b] (%)
1-5			*t*Bu	**1a**, 85
			Cy	**2a**, 96
			*n*Bu	**3a**, 98
			Ph	**4a**, 91[b]
			Me	**5a**, 70
6-9			*t*Bu	**6a**, 99
			Cy	**7a**, 95
			*n*Bu	**8a**, *93*
			Ph	**9a**, 99[b]
10-13			*t*Bu	**10a**, 83[c]
			Cy	**11a**, 72[c]
			*n*Bu	**12a**, 74[c]
			Ph	**13a**, 75[b,c]
14				**14a**, 70[c]
15-17			*t*Bu	**15a**, 78[c]
			Cy	**16a**, 85[c]
			*n*Bu	**17a**, 77[c]
18				**18a**, 82
19-20			*t*Bu	**19a**, 75[c]
			Cy	**20a**, 70[c]
21				**21a**, 61[c]
22			*n*Bu	**22a**, 91

[a] Reaction conditions: 1 mmol of **1**, 1 ml of THF.
[b] Determined by GC analysis using 1,3,5-trimethylbenzene as an internal standard. [c] Isolated yields. Cy = cyclohexyl

The scope of this catalytic system was explored under the optimized reac tion conditions (Table 3.2). While the present work focuses on the coupling of secondary and tertiary alkyl Grignard reagents, the same method could be used to couple primary alkyl or phenyl Grignard reagents in high yields. All the Grignard reagents except phenyl magnesium chloride gave good to excell ent yields under the optimized reaction conditions. In the reactions with Ph MgCl (entries 4, 9, and 13), the high yields were obtained in the presence of 20 mol% of Cu NP at 80 ^{o}C for 12 h. Although MeMgCl seemed to be ineffective in the presence of a cobalt catalyst[13], the use of it afforded a good yield (70%) with a 6% recovery of the reactant with our catalytic system (entry 5). For the reactions of 2-bromoethylbenzene and 2-bromoethyl-1,3-dioxane with alkyl Grignard reagents (entries 6-8 and 10), the cross- cou pling reactions went to completion without an additive. Ester and acetal func tional groups were tolerated (entries 10-13 and 14, respectively). A substrate containing an alcohol group was coupled in high yields when 2.5 eqivalents of a Grignard reagent was used (77-85%) (entries 15-17). An olefinic and an ami de groups are also tolerated (entries 18 and 19-20). Interestingly, a phthalimi de group, which is known to be incompatible with the homogeneous copper cata lyst,[11] was tolerated by the Cu NP catalytic system (entry 21). When 1,4-dibr omopentane was used as a substrate, the primary alkylbromo moiety reacts with the *n*-butyl Grignard reagent to give 2-bromononane in high yield (entr y 22). This observation may provide the synthetic utility of the site-selective cross-coupling reaction.

Table 3.3. Optimization of the cross coupling reaction of 2-chloroethylbenzene with *t*-BuMgCl

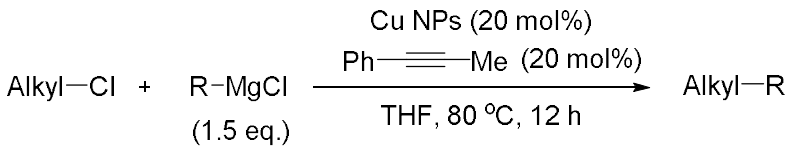


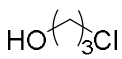
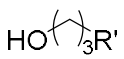
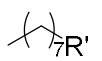
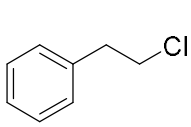
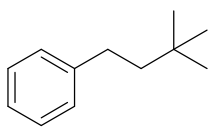
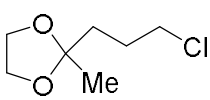
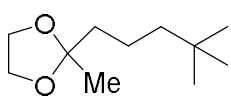
Entry	Cat.	Additive	Grignard(eq.)	Temp.	Time	Yield (%)[a]
1	10	0	1.2	25	1	0
2	10	0	1.2	80	24	13
3	10	10	1.2	40	12	45
4	10	20	1.5	60	12	63
5	10	30	1.5	80	12	61
6	20	20	1.5	60	12	84
7	20	20	1.5	80	6	59
8	20	20	1.5	80	12	96

[a] Determined by GC using 1,3,5-trimethyl benzene as an internal standard.

We next investigated the scope of the Cu NP-catalyzed cross-coupling reactions of alkyl chlorides with alkyl Grignard reagents. Several groups have studied the copper-catalyzed cross coupling of alkyl chlorides with alkyl Grignard reagents. Very different observations were reported depending on the catalytic system used. In the presence of CuCl as a catalyst, alkyl chlorides could not be coupled.[11] However, Kambe et al. reported the cross coupling of simple alkyl chlorides such as *n*-octyl chloride, 1-bromo-6-chlorohexane, and 6-chloro-1-hexene as substrates in the presence of $CuCl_2$ and 1-phenylpropyne.[9] Moreover, in the presence of $CoCl_2$ or Ni-pincer complex as a catalyst, the cross-coupling of alkyl chlorides were inefficient.[13,16] Thus, we examined our catalytic system with alkyl chlorides and optimized the reaction conditions (Table 3.3). Without additive, the reaction gave no product in the presence of 10 mol% of catalyst at 25 ^{o}C (entry 1). The yield was moderate when the reaction conducted in the presence of 20 mol% of additive and 1.5 eq. of Grignard reagent at 60 ^{o}C (entry 4). When the amount of catalyst used was changed from 10 mol% to 20 mol%, the yield was 96 % at 80 ^{o}C (entry 8). With the optimized reaction conditions in hand, we examined the scope of the reaction (Table 3.4). Among primary alkyl chlorides used in this study, alcohol and acetal derivatives (entries 1-3 and 7), *n*-octyl chloride (entries 4 and 5), and (2-chloroethyl) benzene (entry 6) were proved to be good substrates in the reaction with primary, secondary, or tertiary alkyl Grignard reagent. When a cross coupling reaction with PhMgCl was carried out under the same reaction conditions, the expected product was not obtained. Instead, biphenyl was obtained as a major product.

Table 3.4. Cu NP-catalyzed cross-coupling reactions of alkyl chlorides with alkyl Grignard reagent



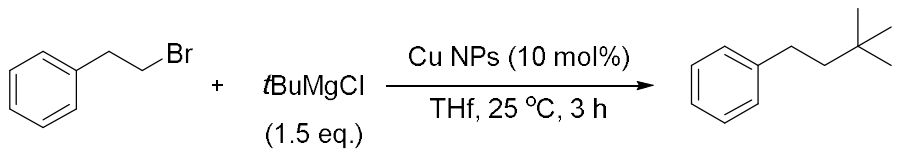
Entry	Substrate	Product	R	Yield[a] (%)
1-3			*t*Bu Cy *n*Bu	**1b,** 84 **2b,** 92 **3b,** 76
4-5			*t*Bu Cy	**4b,** 87[b] **5b,** 88[b]
6				**6b,** 96[b]
7				**7b,** 68

[a] Isolated yields, [b] Determined by GC analysis. Cy = cyclohexyl

3.2.2. Reusability and Mechanistic Investigation

The reusability of the catalyst was also tested in the reaction of (2-bromoeth yl) benzene with *t*BuMgCl (table 3.5). After the reaction was complete, the ca talyst was separated from the reaction mixture by centrifugation, washed wit h diethyl ether and dichlorometane and dried *in vaccuo*. The recovered catal yst was reused in the next runs under the same reaction conditions. The res ults indicate that there is no appreciable difference in the yields of the prod uct even after a fifth run. However, the yield of the sixth cycle decreased t o 90%. The Cu NPs would be reused five times without deactivation, giving a final TON of 49. The elemental analysis (by ICP-AES) of the reaction mixture after completion of the reaction showed that 1.4 % of copper species was leached.[19] The decrease observed in the sixth run may be partly related to the decreas e of the catalytic activity, presumably due to the air oxidation of the catalys t or the formation of MgO films on the copper particles or both (Figure 3.1). [18] Kobayashi et al.[14] also observed significant loss of activity of their copoly mer-incarcerated Ni NP catalysts due to the deposition of magnesium salts o n the NPs. The reusability of the catalyst strongly suggests a heterogeneous mechanism. However, we cannot ignore the possibility of a homogeneous re action due to the detection of copper species in reaction mixture.

Table 3.5. Reuse of catalysts



Entry	Catalyst	Yield[a] (%)
1	1st run	99
2	2nd run	99
3	3rd run	99
4	4th run	99
5	5th run	99
6	6th run	90

[a] Determined by GC using 1,3,5-trimethyl benzene as an internal standard.

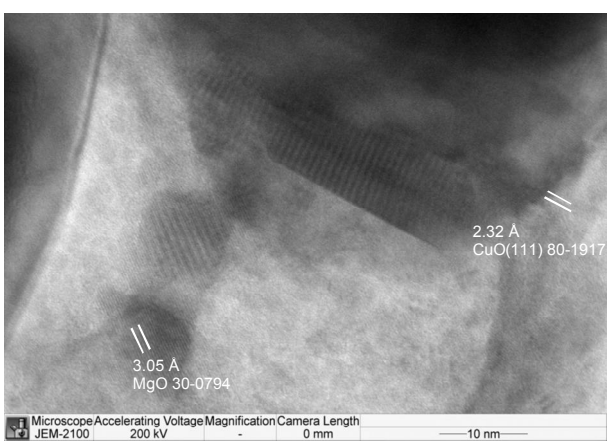
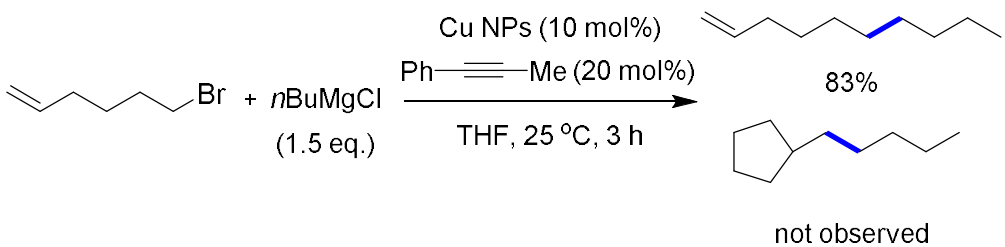
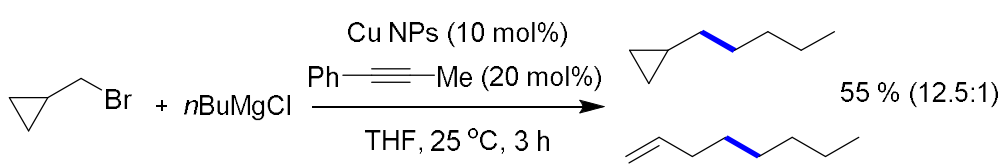


Figure 3.1. HRTEM images of Cu NP catalyst (after 6th run)

In the reaction of (2-bromoethyl) benzene, the addition of an alkyne additive was not required. However, in other cases, the addition of an alkyne additive was necessary. The role of the alkyne additive in the present catalytic reaction has not yet been clarified. Kambe et al.[9,20] suggested that the coordination of alkynes to the copper prevents the decomposition of thermally unstable alkylcopper intermediates. Two decades ago, a time-resolved study of gas-phase reactions of copper atoms with dimethylacetylene (DMA) had undertaken by Mitchell et al.[21] According to their report, CuL and CuL_2 (L = DMA) complexes were formed by Cu + L reactions and were characterized as π-complexes.[21,22] Thus it seems that the role of the alkyne additive is to stabilize reactive alkylcopper intermediates, as Kambe et al. suggested.[9]





Scheme 3.3. Radical clock experiment to identify reaction mechanism

In order to gain some insight into the reaction mechanism, 6-bromo-1-hexene and (bromomethyl)cyclopropane and were reacted with *n*-BuMgCl (Scheme 3.3). In the reaction of 6-bromo-1-hexene with *n*-BuMgCl, 1-decene was formed, but no

cyclized product was observed. However, in the case of (bromomethyl)cyclopropane, pentylcyclopropane and 1-octene were obtained in a ratio of 12.5:1 with a total 55 % yield. These observations indicate that the coupling reaction occur mainly via an S_N2 mechanism.[9,11] In addition, the Cu NP-catalyzed cross-couplings undergo a minor radical pathway. It has been reported[23] that the rearrangement products were observed in the reaction of activated haloalkanes with alkenes in the presence of copper metal.

3.3. Conclusion

In this chapter, we have developed a Cu NP-based cross-coupling method that is remarkably simple and general. The Cu NPs used in this study are comm ercially available and the catalytic system doesn't need any pretreatment or preformed supports and ligands. The catalytic system is quite effective for th e cross-coupling of primary alkyl bromides or chlorides with alkyl or aryl G rignard reagents. In view of the broad scope of the substrates, functional gro up tolerance, high reaction efficiencies, high product yields, and reusability, t he Cu NP-catalyzed cross-coupling reaction can be expected to find wide sy nthetic applications.

3.4. Experimental Section

Materials

All solvents were dried and distilled according to standard methods before use. Solvents utilized in this work were obtained from Samchun Pure Chemicals (hexanes, ethyl acetate, diethyl ether, dichloromethane, tetrahydrofuran, and acetone).

Copper nanoparticles (5~7 nm, 25~40 nm, and 40~60 nm) were purchased from SkySpring Nanomaterials, Inc. (2935 Westhollow Dr., Houston, TX 77082, USA). Copper(II) oxide nanoparticle were purchased from Aldrich.

Tetrahydrofuran (THF) and toluene were dried over Na/benzophenone and distilled under nitrogen. *n*-Hexane and diethyl ether were used without further purification. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, or TCI and were used as received. 6-Bromo-N,N-diethylhexanamide[1](Table 1, entries 20-21) were prepared according to literature procedures. *Tert*-butylmagnesium chloride (2.0 M solutions in diethyl ether), cyclohexylmagnesium chloride (2.0 M solutions in diethyl ether), *n*-butylmagnesium chloride (2.0 M solutions in THF), methylmagnesium chloride (3.0 M soultions in THF) and phenylmagnesium chloride (2.0 M solutions in THF) were purchased from Aldrich. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254). The TLC plates were visualized by UV-light (254 nm) and treatment with acidic *p*-anisaldehyde and $KMnO_4$ stain followed by gentle heating. Workup procedures were done in air. Flash column chromatography was carried out on Merck 60 silica gel (230 – 400 mesh).

Characterization

^{1}H and ^{13}C NMR spectra were recorded with Agilent 400-MR DD2 (400 MHz and 100 MHz, respectively) spectrometer. ^{1}H NMR spectra were taken in $CDCl_3$ and were referenced to residual TMS (0 ppm) and reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.00 ppm). High-Resolution Mass Spectra were obtained at the Korea Basic Science Institute (Daegu, South Korea) on a Jeol JMS 700 high resolution mass spectrometer. GC-MS analyses were performed at NICEM with a Perkin-Elmer Clarus 680GC / 600T with a DB-5MS column (length: 30 m, ID: 0.25 mm, FT: 0.5 μm, Column Program: starting from 40 ^{o}C, 3 min hold, 10 ^{o}C/min to 310^{o}C, 10 min hold). Inductively coupled plasma atomic emission spectroscopy (ICP-AES) was obtained at the National Center for Inter-University Facilities (Seoul National University, South Korea) on an OPTIMA 4300DV, Perkin-Elmer (Argon Plasma, 6000 K). The nanoparticles were characterized by high-resolution transmission electron microscopy (JEOL JEM-2100). X-Ray Diffraction (XRD) data were obtained at the Research Institute of Advanced Material (Seoul National University, South Korea) on a Brucker New D8 Advance.

Synthesis

Procedure for the entries reported Table 2.2 from alkyl bromides

Reactions were performed in a schlenk tube equipped with a stirring bar and capped with a rubber septum. The followings were placed in the tube in order: 7 mg (c.a. 10 mol%) of catalyst (in a glove box), 1 mmol of alkyl bromide**,** 20 mol% (24 μL) of 1-phenylpropyne, 1.5 eq. (0.75 mL) of alkyl Grignard reagents and 1 mL of THF. The mixture was stirred at room temperature for 3 h. The reaction

mixture was extracted with aqueous NH_4Cl solution and diethyl ether and dried over $MgSO_4$, filtered and finally evaporated under reduced pressure. The mixture was purified by flash chromatography on silica gel (*n*-hexane/diethyl ether) to afford the product. Products that were not isolated by column chromatography were determined by GC analysis using 1,3,5-trimethylbenzene as an internal standard.

10a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (t, *J* = 5.2 Hz, 1 H), 4.03 (dd, *J* = 10.8, 5.0 Hz, 2 H), 3.68 (td, *J* = 12.4, 2.4 Hz, 2 H), 2.07 – 1.94 (m, 1 H), 1.54 – 1.47 (m, 2 H), 1.28 – 1.24 (m, 1 H), 1.23 – 1.18 (m, 2 H), 0.80 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.0, 66.8, 37.8, 31.5, 30.5, 29.7, 29.1, 25.8, 22.5, 14.0; HRMS (FAB) calc. for $[C_{10}H_{21}O_2, M+H]^+$ 173.1542, found 173.1543

11a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (t, *J* = 5.2 Hz, 1 H), 4.02 (dd, *J* = 10.9, 4.9 Hz, 2 H), 3.68 (td, *J* = 12.3, 2.1 Hz, 2 H), 2.06 – 1.94 (m, 1 H), 1.67 – 1.57 (m, 4 H), 1.55 – 1.49 (m, 2 H), 1.29 – 1.02 (m, 8 H), 0.85 – 0.78 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.7, 66.8, 37.4, 33.1, 32.6, 31.4, 26.5, 26.2, 25.8; HRMS (FAB) calc. for $[C_{12}H_{23}O_2, M+H]^+$ 199.1698, found 199.1696

12a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (t, *J* = 5.2 Hz, 1 H), 4.05 – 3.99 (m, 2 H), 3.72 – 3.64 (m, 2 H), 2.07 – 1.94 (m, 1 H), 1.54 – 1.48 (m, 2 H), 1.33 – 1.17 (m, 9 H), 0.80 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.3, 66.7, 35.1, 31.6, 29.1, 25.8, 23.8, 22.4, 13.9; HRMS (FAB) calc. for $[C_{10}H_{21}O_2, M+H]^+$ 173.1542, found 173.1539.

13a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 7.20 – 7.13 (m, 3H), 4.48 (t, *J* = 5.2 Hz, 1H), 4.11 – 4.05 (m, 2H), 3.74 – 3.67 (m, 2H), 2.71 (dd, *J* = 9.1, 7.0 Hz, 2H), 2.11 – 2.00 (m, 1H), 1.93 – 1.88 (m, 2H), 1.31 – 1.26 (m, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 141.6, 128.3, 128.2, 125.6, 101.3, 66.7, 36.5, 29.9, 25.7; HRMS (FAB) calc. for $[C_{12}H_{17}O_2, M+H]^+$ 193.1229, found 193.1225.

14a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (td, *J* = 6.7, 0.9 Hz, 2 H), 1.97 (d, *J* = 1.2 Hz, 3 H), 1.59 – 1.53 (m, 2 H), 1.27 – 1.19 (m, 4 H), 1.09 – 1.07 (m, 2 H), 0.79 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 64.6, 44.0, 30.2, 29.3, 28.6, 26.8, 24.2, 20.9; HRMS (EI) calc. for $[C_{11}H_{23}O_2, M+H]^+$ 187.1698, found 187.1770.

15a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (t, *J* = 6.7 Hz, 2 H), 2.52 (s, 1 H), 1.54 – 1.46 (m, 2 H), 1.29 – 1.15 (m, 4 H), 1.13 – 1.07 (m, 2 H), 0.79 (s, 9 H); ^{13}C NMR (100 MHz, CDl_3) δ 62.7, 44.1, 32.8, 30.2, 29.3, 26.6, 24.3; HRMS (EI) calc. for $[C_9H_{19}O, M-H]^+$ 143.1436, found 143.1435

16a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (t, *J* = 6.7 Hz, 2 H), 2.50 (s, 1 H), 1.65 – 1.54 (m, 5 H), 1.51 – 1.44 (m, 2 H), 1.26 – 1.21 (m, 4 H), 1.17 – 1.03 (m, 6 H), 0.83 – 0.76 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.7, 37.5, 37.4, 33.3, 32.7, 26.7, 26.6, 26.3, 26.0; HRMS (EI) calc. for $[C_{11}H_{21}O, M-H]^+$ 169.1592, found 169.1590.

17a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (t, *J* = 6.7 Hz, 2 H), 2.41 (s, 1 H), 1.53 – 1.44 (m, 2 H), 1.28 – 1.17 (m, 12 H), 0.81 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.7, 32.7, 31.8, 29.5, 29.4, 29.2, 25.7, 22.6, 14.0; HRMS (EI) calc. for $[C_9H_{19}O, M-H]^+$ 143.1436, found 143.1437.

19a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 (q, *J* = 7.1 Hz, 2 H), 3.17 (q, *J* = 7.2 Hz, 2 H), 2.17 – 2.13 (m, 2 H), 1.56 – 1.48 (m, 2 H), 1.20 – 1.11 (m, 4 H), 1.07 – 1.01 (m, 5 H), 0.97 (t, *J* = 7.1 Hz, 3 H), 0.72 (s, 9 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 43.8, 41.7, 39.8, 32.9, 30.2, 30.0, 29.1, 25.3, 24.1, 14.2, 13.0; HRMS (FAB) calc. for $[C_{14}H_{30}NO, M+H]^+$ 228.2327, found 228.2329

20a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.23 – 3.17 (m, 2 H), 3.16 – 3.09 (m, 2 H), 2.15 – 2.06 (m, 2 H), 1.57 – 1.38 (m, 7 H), 1.20 – 1.09 (m, 4 H), 1.09 – 0.95 (m, 9 H), 0.93 (td, *J* = 7.1, 2.7 Hz, 3 H), 0.73 – 0.61 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 41.6, 39.6, 37.3, 37.0, 33.1, 32.8, 29.5, 26.4, 26.3, 26.1, 25.2, 14.0, 12.7; HRMS (FAB) calc. for $[C_{16}H_{32}NO, M+H]^+$ 254.2484, found 254.2485.

21a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.5 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 7.47 (td, *J* = 7.5, 1.1 Hz, 1 H), 7.39 (td, *J* = 7.4, 0.8 Hz, 1 H), 4.12 – 4.01 (m, 2 H), 3.68 (ddd, *J* = 10.2, 7.9, 6.6 Hz, 1 H), 3.40 – 3.32 (m, 1 H), 0.94 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 148.5, 132.8, 132.4, 129.3, 123.9, 123.5, 105.3, 69.2, 46.21, 39.5, 25.4; HRMS (FAB) calc. for $[C_{14}H_{18}NO_2, M+H]^+$ 232.1338, found 232.1340

7b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (q, *J* = 5.7 Hz, 4 H), 1.52 (dd, *J* = 10.3, 6.0 Hz, 2 H), 1.33 – 1.26 (m, 2 H), 1.25 (s, 3 H), 1.13 – 1.07 (m, 2 H), 0.81 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.1, 64.5, 44.3, 40.1, 30.3, 29.4, 23.7, 19.1; HRMS (FAB) calc. for $[C_{11}H_{23}O_2, M+H]^+$ 187.1698, found 187.1696

3.5. References

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18. According to the TEM image and XRD data of the purchasing copper nanoparticles, the lattices of Cu nanoparticles were observed with those of Cu_2O nanoparticles.
19. For comparison, the same amount of Cu present in a soluble catalyst $CuCl_2$ under our reaction conditions gave a trace amount of product
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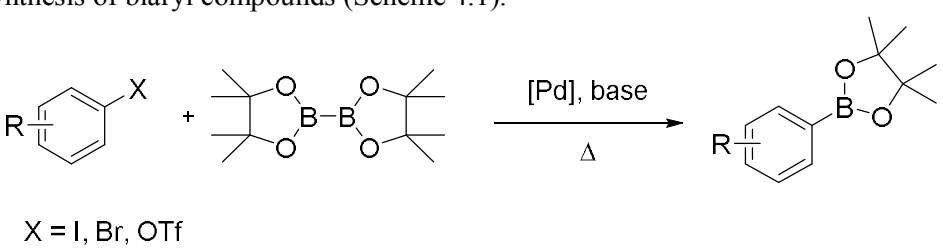
Chapter 4. Copper Nanoparticle-Catalyzed Borylation of Alkyl Bromides with Organodiboron Compound

4.1. Introduction

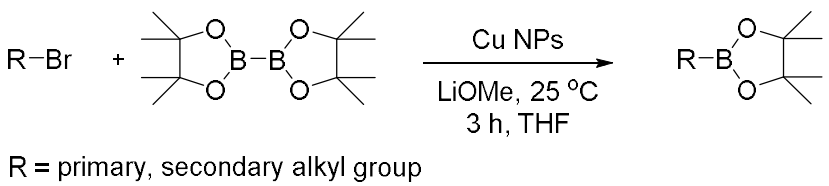
In Chapter 3, we presented the results of copper nanoparticle-catalyzed carbon-carbon bond cross-coupling reactions of alkyl halides with Grignard reagents. Among the numerous catalytic cross-coupling reactions, the Suzuki–Miyaura cross-coupling reaction, catalyzed by a palladium(0) complex, and where the coupling partners are a boronic acid and a halide, shared the Nobel Prize for Chemistry 2010 because it was one of the most significant methodologies for the synthesis of biaryl compounds (Scheme 4.1).[1]



Scheme 4.1. Suzuki-Miyaura cross-coupling reaction

Over the past decades, the synthetically useful organoboron-containing compounds have been actively developed.[2] For several years, the transition metal-catalyzed borylation of the C-H bond has attracted much attention as an alternative method for the synthesis of the C-B bond.[3] Among the different transition metal–catalysts used for borylation reactions, palladium, nickel, and copper complexes are by far the most widely studied, mainly because of their extensive applicable scope, and compatibility with many functional groups.[4-6] However, most of the catalytic systems involve the use of toxic ligands such as phosphine compounds. Therefore, there is a need for the development of environment-friendly and economically more convenient catalytic systems. In this regard, the use of copper-

based catalysts[5] is particularly attractive because they are inexpensive, readily available, and environmentally friendly. The use of an inexpensive Cu catalyst for the borylation of alkyl halides at room temperature was reported by Liu and Ito et al.[6, 7] In 2012, the ligand-free copper-catalyzed borylation of benzyl halides with bis(pinacolato)diboron in DMF at 80 °C was reported by Yan.[5c] Previous studies on the copper-catalyzed cross-coupling reactions[5,6] including our work in chapter 3, provided important motives to use copper nanoparticles (Cu NPs) as catalysts in the coupling reactions of alkyl halides with diboron reagents (Scheme 4.2).



Scheme 4.2. Synthesis of alkylboronate via copper-nanoparticle catalysed borylation of alkyl bromide

It has been recently reported[8] that copper(II) oxide nanoparticles (CuO NPs) supported on magnesia exhibits complete chemoselectivity towards the monoborylation of alkynes in the presence of alkenes and triphenylphosphine. However, the catalysis of such transformations by Cu NPs has not been reported. Therefore, we decided to study the use of Cu NPs in the borylation of unactivated alkyl halides with alkoxy diboron compounds. It was found that Cu NPs were quite effective catalysts in the borylation of primary and secondary alkyl bromides with bis(pinacolato)diboron. Chapter 4 will discuss the copper nanoparticle-catalyzed reactions. Cu NPs could efficiently catalyze the cross-coupling of alkyl boronate with nonactivated alkyl bromides in the absence of phosphines at room temperatures.

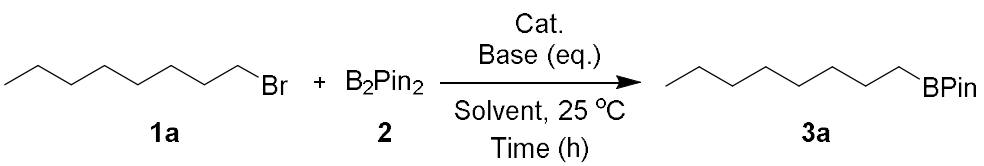
4.2. Results and Discussion

4.2.1. Optimization of reaction conditions

Based on the results of Chapter 3 and previously reported papers,[6,7] temporary reaction conditions were settled. The reaction of 1-bromooctane (**1a**) with bis(pinacolato)diboron (**2**) to produce pinacol alkylboronate (**3a**) was chosen as a model reaction in Table 4.1. We carried out the optimization of the catalyst system. The same catalyst used in our previous study[9] and Chapter 3 was used. The treatment of 1a with 2 in the presence of 15 mol% of Cu NPs and 2 equiv of LiO*t*Bu in DMF at 25 ^{o}C for 18 h was found to produce the corresponding alkylboronate 3a in a good yield (99%, entry 1). The reaction time could be decreased to 3 h without any loss in the yield (99%, entry 2). To improve the yield, different bases such as LiOMe, K_2CO_3, NaOH, and NaOMe were studied (entries 3 ~ 6). It was observed that the base LiOMe afforded good yields of the desired product (90%). However, other bases such as K_2CO_3, NaOH, and NaOMe were not as effective (yields: 32–69%). LiO*t*Bu was found to be the best base giving a yield of 99 % (entry 2), but it was effective only for normal alkyl bromides. Thus, we chose LiOMe as the base in our reaction. The effect of various solvents on the reaction system was also examined (entries 7–9). It was observed that solvents, such as THF, toluene, and MeCN, were proven to be inefficient for this transformation, but the reasons for this are not very clear. DMF was found to give the best results and was used for further studies. The necessity of Cu NPs in the reaction was confirmed by the observation that no reaction was observed in their absence (entry 10). We also examined other metal compounds such as $Pd(OAc)_2$, $NiCl_2$, and CuO NPs as a catalyst under the optimized reaction conditions (entries 11–13). In the presence of $Pd(OAc)_2$, no reaction was observed. However, in the

presence of $NiCl_2$ and CuO NPs, the formation of 3a was observed in 3% and 31% yields, respectively. Although our previous study[9] showed that CuO NPs were also an active catalyst in the C-C coupling reaction in the presence of Grignard reagents, the borylation reaction using CuO NPs was sluggish. Among the catalysts studied, no other catalysts afforded a higher yield than Cu NPs used. The possibility of contamination by palladium or nickel in the catalytic reaction was eliminated.[10]

Table 4.1. Screening reaction conditions[a]



Entry	Cat.	Cat. (mol%)	Base	Solvent	Time	Yield[b] (%)
1	Cu NP	15	LiO*t*Bu	DMF	18	99
2	Cu NP	15	LiO*t*Bu	DMF	3	99
3	Cu NP	15	LiOMe	DMF	3	90
4	Cu NP	15	NaOMe	DMF	3	32
5	Cu NP	15	K_2CO_3	DMF	3	43
6	Cu NP	15	NaOH	DMF	3	69
7	Cu NP	15	LiOMe	THF	3	0
8	Cu NP	15	LiOMe	MeCN	3	0
9	Cu NP	15	LiOMe	Toluene	3	0
10	No cat.		LiO*t*Bu	DMF	3	0
11	$Pd(OAc)_2$	15	LiOMe	DMF	3	0
12	$NiCl_2$	15	LiOMe	DMF	3	3
13	CuO NP	15	LiOMe	DMF	3	31

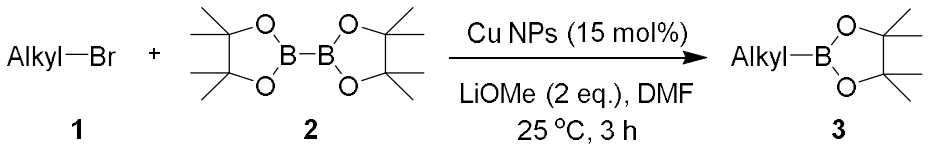
[a] Reaction conditions: **1a** (0.5 mmol), 15 mol% of catalyst, 1.5 eq. of B_2Pin_2, 2 eq. of base and 1 mL of solvent.
[b] Determined by GC analysis using 1,3,5-trimethylbenzene as an internal standard.

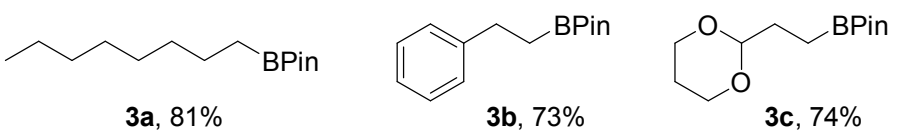
4.2.2. Substrate Scope and Mechanistic Experiment

With the optimized conditions in hand, we next investigated the substrate scope of the borylation of the alkyl bromides using 2 (Table 4.2).

The yield ranged from 55% to 93%. The presence of functional groups (**3a-3k**), such as acetal, ester, hydroxy, amide, and cyano groups, and an ether linkage in the starting alkyl bromides **1** did not interfere with the outcome of the borylation with **1**. In particular, it is notable that even without a protecting group, the borylation reaction proceeds in the presence of a hydroxyl group (**3g**).[6] Compounds containing heterocyclic arenes, such as pyran and indole (**3i-3j**) are good substrates for the borylation. Interestingly, (2-bromoethoxy)benzene, which is known to undergo a C-O bond cleavage in the reaction with a Grignard reagent in the presence of Cu NPs,[9] afforded a high yield (93%) of the borylation product (entry 4). Compared to a homogeneous copper system (CuI and PPh3),[7] the Cu NP system showed a higher activity for some substrates having functional groups such as a hydroxyl, or an amide, but showed lesser activity for other substrates having nitrile, indole, or benzyl groups. However, it seems that the overall reactivity of the Cu NP system seemed to be similar to that of the homogeneous copper system.

Table 4.2. Reaction scope of substrates[a,b]

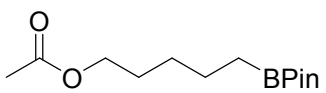




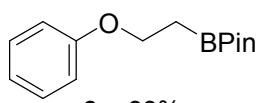
3a, 81%

3b, 73%

3c, 74%



3d, 81%



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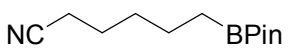

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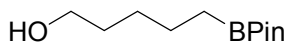
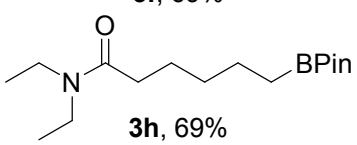
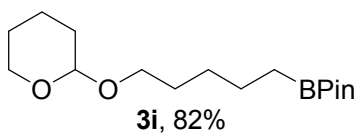


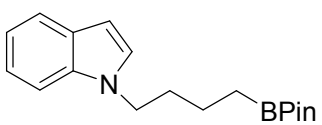
3g, 64%



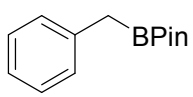
3h, 69%



3i, 82%



3j, 55%



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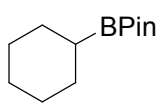
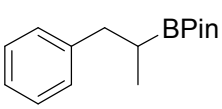
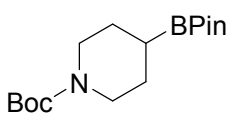


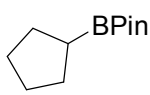
3l, 78%



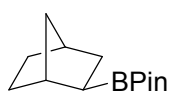
3m, 82%



3o, 75%



3p, 62%



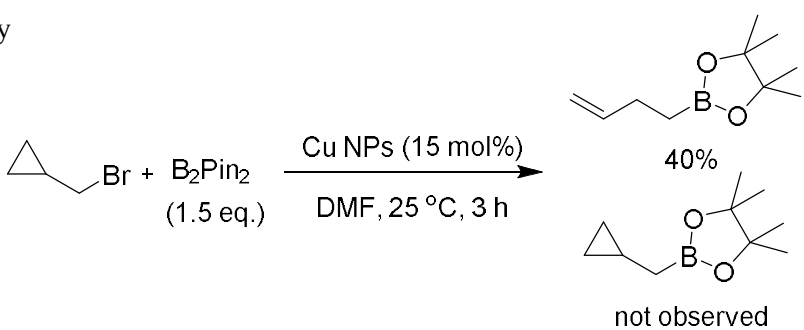
3q, 71%

[a] Reaction conditions: **1** (0.5 mmol), 15 mol% of catalyst, 1.5 eq. of B_2Pin_2, 2 eq. of LiOMe, 3 h and 1 mL of DMF.

[b] Yield of Isolated Product. [c] Reaction time was 6 h.

We also studied the borylation of secondary alkyl bromides under our optimized reaction conditions (3l-3q). For the borylation of *exo*-2-bromonorbornane, an overall retention of configuration was observed (3q).[6] Unactivated secondary alkyl halides could be borylated with good yields (62–82%). Cyclic and acyclic secondary bromides were easily borylated and a protected amine was also a good substrate. For cyclohexyl bromide, the yield was 78% at 25 ^{o}C for 3 h. This yield was higher than that (60%) observed in the presence of CuI and PPh_3 at 25 ^{o}C for 24 h by Liu et al[6] although they observed a 79% yield at a higher reaction temperature (37 ^{o}C). Thus, our catalytic system was highly effective for the borylation of primary and secondary alkyl bromides, but primary alky chlorides and tertiary alkyl halides were found to be inert under our reaction conditions.

To validate the reaction mechanism further, we carried out an experiment (Scheme 4.3). When the borylation of cyclopropylmethyl bromide was carried out in the presence of Cu NPs, 3-butenylboronate was isolated in 40% yield and no simple boryl substitution product was observed. In contrast to the case of Cu NP-catalyzed coupling reaction in the presence of a Grignard reagent, [9] the observation of the ring-opening product provided an evidence for the formation of a radical intermediate, which suggests that the reaction probably proceeds via a radical pathway



Scheme 4.3. Radical clock experiment for verify the reaction mechanism

4.3. Conclusion

Following the results of chapter 3, we have developed a remarkably simple and general Cu NP-catalyzed borylation reaction under phosphine-free conditions. The Cu NPs used in Chapter 3 are commercially available, and the catalytic system does not require any pretreatment or preformed supports and ligands. The catalytic system is quite effective for the borylation of unactivated primary and secondary alkyl bromides with organodiboron compounds. In view of the broad substrate scope, functional group tolerance, high reaction efficiencies, and high product yields, the Cu NP-catalyzed cross-coupling reaction can be expected to find wide synthetic applications. The reaction might be proceeded via radical pathway due to the results of radical clock experiment.

4.4. Experimental Section

Materials

All solvents were dried and distilled according to standard methods before use. Solvents utilized in this work were obtained from Sigma-Aldrich (anhydrous *N*,*N*-dimethylformamide) and Samchun Pure Chemicals (hexanes, ethyl acetate, diethyl ether, dichloromethane and acetone).

Copper nanoparticles (25~40 nm) were purchased from SkySpring Nanomaterials, Inc. (2935 Westhollow Dr., Houston, TX 77082, USA). Copper(II) oxide nanoparticle were purchased from Sigma-Aldrich.

n-Hexane, diethyl ether and ethyl acetate were used without further purification. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, or TCI and were used as received. 6-Bromo-N,N-diethylhexanamide[11] (Table 1, entries 20-21), 2-(6-bromohexyloxy)tetrahydro-2H-pyran and 1-(4-bromobutyl)-1H-indole[12] were prepared according to literature procedures. Bis(pinacolato)diboron were purchased from Sigma-Aldrich. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254). The TLC plates were visualized by UV-light (254 nm) and treatment with acidic *p*-anisaldehyde and $KMnO_4$ stain followed by gentle heating. Workup procedures were done in air. Flash column chromatography was carried out on Merck 60 silica gel (230 – 400 mesh).

Characterization

^1H and ^{13}C NMR spectra were recorded with Agilent 400-MR DD2 (400 MHz and 100 MHz, respectively) spectrometer. ^1H NMR spectra were taken in $CDCl_3$ and were referenced to residual TMS (7.26 ppm) and reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.00 ppm). ^{11}B NMR spectra

were recorded with Jeol JNM-LA400 with LFG (128 MHz, respectively) at NICEM. High-Resolution Mass Spectra were obtained at the Korea Basic Science Institute (Daegu, South Korea) on a Jeol JMS 700 high resolution mass spectrometer. GC-MS analyses were performed with a HP-6890 series with a HP-5 capillary column (30 m x 0.25 mm; coating thickness 0.25 μm) and Agilent 5973 Network Mass Selective detector. Analytical condition – initial temperature: 50 ^{o}C, raising temperature 10 ^{o}C / min, final temperature: 280 ^{o}C, He gas, Pressure : 7.56 psi, Total flow : 53.7 mL / min.

Synthesis

Procedure for the entries reported Table 3.2 from alkyl bromides

Reactions were performed in a schlenk tube equipped with a stirring bar and capped with a rubber septum. The followings were placed in the tube in order: 5 mg (c.a. 15 mol%) of catalyst (stored in a glove box), 0.5 mmol of alkyl bromide, 2 equiv (0.75 g) of base, 1.5 equiv (0.19g) of bis(pinacolato)diboron and 1 mL of DMF. The mixture was stirred at room temperature for 3 h. The reaction mixture was filtered over a silica gel pad using ethyl acetate and diethyl ether and the filtrate was evaporated under reduced pressure. The concentrated reaction mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate) to afford the product.

3a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 – 1.34 (m, 2 H), 1.31 – 1.23 (m, 10 H), 1.23 (s, 12 H), 0.85 (t, J = 6.9 Hz, 3 H), 0.77 – 0.72 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.8, 32.4, 31.9, 29.4, 29.2, 24.8, 24.0, 22.7, 14.1, 11.2; ^{11}B NMR (128 MHz, CDCl3) δ 33.3; HRMS (EI) calc. for $[C_{14}H_{29}BO_2, M]^{+}$ 240.2261, found 240.2257

3b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (t, J = 5.1 Hz, 1 H), 4.09 – 4.03 (m, 2 H), 3.76 – 3.67 (m, 2 H), 2.10 – 1.97 (m, 1 H), 1.69 (td, J = 7.7, 5.2 Hz, 2 H), 1.32 –

1.26 (m, 1 H), 1.21 (s, 12 H), 0.80 (t, J = 7.7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.1, 82.8, 82.8, 66.7, 29.4, 25.8, 24.9, 24.7, 5.3; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.0; HRMS (FAB) calc. for $[C_{12}H_{23}BO_4, M\text{-}H]^+$ 241.1611, found 241.1608

3c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 4 H), 7.19 – 7.12 (m, 1 H), 2.78 – 2.72 (m, 2 H), 1.22 (s, 12 H), 1.18 – 1.12 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 128.1, 127.94, 125.44, 83.03, 29.91, 24.76, 12.95; HRMS (EI) calc. for $[C_{14}H_{21}BO_2, M]^+$ 232.1635, found 232.1637

3d: ^{1}H NMR (400 MHz, cdcl$_3$) δ 3.99 (t, J = 6.8 Hz, 2 H), 1.99 (s, 3 H), 1.63 – 1.52 (m, 2 H), 1.44 – 1.35 (m, 2 H), 1.35 – 1.27 (m, 2 H), 1.19 (s, 12 H), 0.76 – 0.70 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 82.7, 64.4, 28.4, 28.2, 24.7, 23.5, 20.9, 11.0; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2; HRMS (FAB) calc. for $[C_{13}H_{25}BO_4, M+H]^+$ 257.1924, found 257.1927

3e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 2H), 6.91 (t, J = 7.6 Hz, 3 H), 4.10 (t, J = 7.8 Hz, 2 H), 1.37 (t, J = 7.8 Hz, 2 H), 1.26 (s, 12 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.0, 129.2, 120.3, 114.6, 83.3, 64.7, 24.7, 12.6; ^{11}B NMR (128 MHz, $CDCl_3$) δ 32.3; HRMS (EI) calc. for $[C_{14}H_{21}BO_3, M]^+$ 248.1584, found 248.1582

3g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (t, J = 7.2 Hz, 2 H), 1.67 – 1.57 (m, 2 H), 1.45 – 1.39 (m, 4 H), 1.21 (s, 12 H), 0.76 (t, J = 7.3 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.8, 83.0, 31.1, 25.0, 24.7, 23.0, 16.9, 10.7; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.0; HRMS (EI) calc. for $[C_{12}H_{22}BNO_2, M]^+$ 223.1744, found 223.1741.

3f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (t, J = 6.5 Hz, 2 H), 1.63 (s, 1 H), 1.54 (dt, J = 13.1, 6.5 Hz, 2 H), 1.45 – 1.38 (m, 2 H), 1.38 – 1.31 (m, 2 H), 1.22 (s, 12 H), 0.77 (t, J = 7.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.9, 62.8, 32.4, 28.3, 24.8, 23.6, 11.0; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3; HRMS (FAB) calc. for

$[C_{11}H_{23}BO_3, M+H]^+$ 215.1819, found 215.1820

3h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.31 (q, *J* = 7.1 Hz, 2 H), 3.25 (q, *J* = 7.1 Hz, 2 H), 2.25 – 2.20 (m, 2 H), 1.59 (dt, *J* = 15.3, 7.6 Hz, 2 H), 1.44 – 1.34 (m, 2 H), 1.34 – 1.24 (m, 2 H), 1.19 (s, 12 H), 1.11 (t, *J* = 7.1 Hz, 3 H), 1.05 (t, *J* = 7.1 Hz, 3 H), 0.73 (t, *J* = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 82.8, 41.9, 39.9, 33.1, 32.3, 25.3, 24.7, 23.8, 14.3, 13.1, 11.1; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.1; HRMS (EI) calc. for $[C_{16}H_{32}BNO_3, M]^+$ 297.2475, found 297.2474

3i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 – 4.52 (m, 1H), 3.88 – 3.80 (m, 1H), 3.68 (dt, *J* = 9.6, 6.9 Hz, 1 H), 3.49 – 3.42 (m, 1H), 3.34 (dt, *J* = 9.6, 6.7 Hz, 1H), 1.84 – 1.74 (m, 1H), 1.71 – 1.63 (m, 1H), 1.61 – 1.45 (m, 6H), 1.43 – 1.30 (m, 4H), 1.20 (s, 12H), 0.74 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 98.7, 82.8, 67.5, 62.2, 30.7, 29.5, 29.0, 25.4, 24.7, 23.8, 19.6, 11.1; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2; HRMS (EI) calc. for $[C_{16}H_{31}BO_4, M-H]^+$ 297.2237, found 297.2236

3j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 1 H), 7.37 (dd, *J* = 8.2, 0.6 Hz, 1 H), 7.25 – 7.19 (m, 1 H), 7.13 – 7.09 (m, 2 H), 6.50 (dd, *J* = 3.1, 0.7 Hz, 1 H), 1.88 (ddd, *J* = 15.1, 11.2, 7.6 Hz, 2 H), 1.50 (dt, *J* = 15.4, 7.7 Hz, 2 H), 1.25 (s, 12 H), 0.85 (t, *J* = 7.7 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 128.5, 127.7, 121.1, 120.8, 119.0, 109.4, 100.7, 83.0, 46.2, 32.6, 24.8, 21.4, 10.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2; HRMS (EI) calc. for $[C_{18}H_{26}BNO_2, M]^+$ 299.2057, found 299.2059

3k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.18 (m, 4 H), 7.14 – 7.11 (m, 1 H), 2.30 (s, 2 H), 1.24 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.9, 128.2, 124.8, 83.3, 24.7, 19.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 32.2; HRMS (EI) calc. for $[C_{13}H_{19}BO_2, M]^+$ 218.1478, found 218.1481

3l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 – 1.50 (m, 5 H), 1.42 – 1.24 (m, 5 H), 1.22

(s, 12 H), 1.01 – 0.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.7, 27.9, 27.1, 26.7, 24.7, 22.1; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2; HRMS (EI) calc. for $[C_{12}H_{23}BO_2, M]^+$ 210.1791, found 210.1792

3m: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 4 H), 7.16 – 7.11 (m, 1 H), 2.80 (dd, *J* = 13.6, 7.6 Hz, 1 H), 2.54 (dd, *J* = 13.6, 8.3 Hz, 1 H), 1.43 – 1.34 (m, 1 H), 1.18 (s, 12 H), 0.97 (d, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 128.8, 127.9, 125.5, 82.9, 38.9, 24.6, 18.9, 15.2; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.4; HRMS (EI) calc. for $[C_{15}H_{23}BO_2, M]^+$ 246.1791, found 246.1789

3o: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 – 3.67 (m, 2 H), 2.95 – 2.80 (m, 2 H), 1.62 – 1.54 (m, 2 H), 1.48 – 1.40 (m, 2 H), 1.39 (s, 9 H), 1.18 (s, 12 H), 1.09 – 1.01 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 83.0, 78.9, 44.3(broad), 28.4, 26.8, 24.6, 19.7; ^{11}B NMR (128 MHz, $CDCl_3$) δ 32.8; HRMS (EI) calc. for $[C_{16}H_{30}BNO_4, M]^+$ 311.2268, found 311.2271

3p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 – 1.68 (m, 2 H), 1.61 – 1.53 (m, 2 H), 1.52 – 1.38 (m, 4 H), 1.21 (s, 12 H), 1.17 – 1.11 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.7, 28.5, 26.8, 24.7, 22.0; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7; HRMS (EI) calc. for $[C_{11}H_{21}BO_2, M]^+$ 196.1635, found 196.1636

3q[13,14]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 – 2.24 (m, 1 H), 2.22 – 2.17 (m, 1 H), 1.58 – 1.45 (m, 3 H), 1.38 – 1.23 (m, 3 H), 1.20 (s, 12 H), 1.18 – 1.10 (m, 2 H), 0.89 – 0.83 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.7, 38.7, 38.1, 36.6, 32.2, 32.1, 29.2, 24.7; ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2; HRMS (EI) calc. for $[C_{13}H_{23}BO_2, M]^+$ 222.1791, found 222.1793

4.5. References

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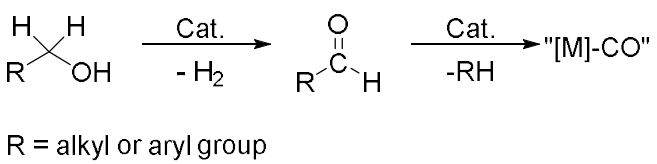
Part II. Rhodium-Catalyzed Carbonylation Reaction Using Alcohol as the Carbon Monoxide Source

Chapter 5. Rhodium-Catalyzed Synthesis of Esters from Aryl Iodides and Alcohols: Use of Alcohols with/without the Assistance of Aldehydes as Carbon Monoxide and Nucleophile Sources

5.1. Introduction

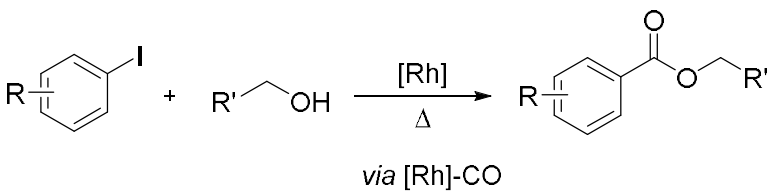
In part I, we discussed about transition metal nanoparticle-catalyzed bond forming reaction including nitrogen-nitrogen, carbon-carbon, and carbon-boron bond. Inspired by the work in Chapter 2, we decided to expand our research program to use alcohol as a reaction partner with transition metal catalyst. We found that alcohol could act metal-hydride source in the presence of ruthenium nanoparticle. Based on this result, we hypothesized that aldehyde, dehydrogenated compound of an alcohol, would be a reliable carbon monoxide source in the presence of transition metal catalysts (Scheme 5.1). Thus, we investigated a series of carbonylation reactions.



Scheme 5.1. Transition metal-catalyzed alcohol activation

Since the first report by Heck et al. on the palladium-catalyzed reaction of carbon monoxide with aryl halides and alcohols or amines,[1] transition metal catalyzed cross-coupling reactions have been developed as a valuable method for creating carbon-carbon bonds.[2] In particular, the Rhodium-catalyzed carbonylation with a variety of substrate has been studied.[3] These reactions require the addition of external CO gas to the substrate, and are typically carried out with carbon monoxide gas. However, the use of carbon monoxide is not recommendable due to

its toxicity and difficulty to handle. Thus, the use of CO-releasing reagents, such as formic acid derivatives[4], oxiranes,[5] and aldehyde[6] has been studied extensively. In 2015, Jun et al. reported[7] the Pd/C-catalyzed carbonylative esterification of a primary alcohol with aryl chlorides in the presence of NaF. Previously, we reported the use of an alcohol as a CO source in the rhodium-catalyzed Pauson-Khand reaction of enynes[8] and as a source of hydrogen in the Rh-catalyzed reductive cyclization of enynes.[9] Thus, in the presence of a rhodium catalyst, an alcohol can be used as a CO or hydrogen source as well as a reaction medium. We therefore decided to explore the use of an alcohol as a CO and nucleophile source, in a reaction with aryl iodides, during the synthesis of esters (Scheme 5.2).



Scheme 5.2. Rhodium-catalyzed esterification of aryl iodides

We studied the alkoxycarbonylation of an aryl iodide with an alcohol in the presence of a base and a rhodium catalyst. This led to the discovery of a rhodium-catalyzed, CO-gas-free alkoxycarbonylation reaction of aryl iodide. The reaction occurred in the presence of an alcohol with/without an aldehyde. The alcohol acted as both a CO and nucleophile source to afford an alkoxycarbonylated product. Chapter 5 will represent the results.

5.2. Results and Discussion

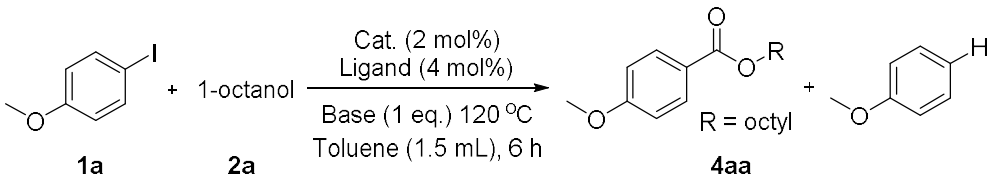
5.2.1. Optimization of reaction conditions

The reaction of 4-iodoansiole (**1a**) with 1-octanol (**2a**) in the presence of $[Rh(COD)Cl]_2$ (2 mol%) and DPEPhos [DPEPhos = (oxydi-2,1-phenylene)bis(diphenylphosphine)] (4 mol%) at 70 ^oC was chosen as the synthetic model. This afforded the alkoxycarbonylation product, octyl 4-methoxybenzoate (**4aa**). Numerous experiments were carried out to improve the yield of products (Table 5.1).

At first, different rhodium compounds and other transition metals were screened (entries 1-8). However, the yield of product was still similar. Other transition metals, such as iridium, palladium, nickel and platinum, gave no product. A variety of phosphine ligands were also tested (entries 9-17). A monodentate phosphine ligand, such as PPh_3, gave a trace amount of product. Instead, a reduction product of aryl iodide, anisole, was obtained in 75 % yield. In the case of a bidentate phosphine ligand, the yield of product was depending upon bite angle of ligand. Dppm, which is the smallest bite angel in table 5.1, gave 95 % yield of the reduction product. Using dppp as a ligand, the product yield is relatively lower than other bidentate phosphine ligands used. However, the reduction product was still a problem in our catalytic reaction.

Depending on the base used, the yield of product was quite different (entries 18-23). For example, DIPEA, which is very common amine base in organic reactions, resulted in a trace amount of products (entry 18). Although a variety of metals, ligands, and bases were screened, the yield of product was still moderate. In order to block the reduction pathway, various additives were added. Moreover, we hypothesized that a metal hydride would make a key role in the reduction pathway. Thus, additional screening experiments were performed (Table 5.2)

Table 5.1. Screening reaction conditions

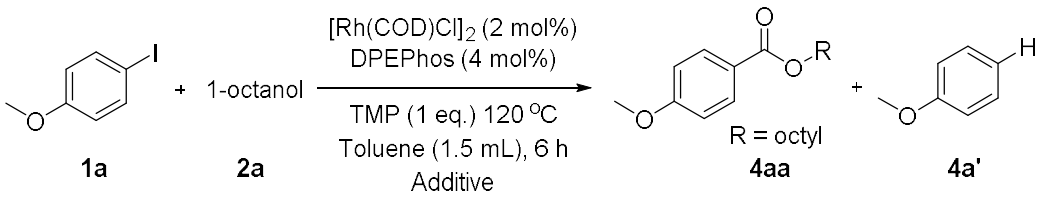


entry	cat (mol %)	Ligand	Base	Temperature	Yield (%)[a,b]
1	$Rh(COD)Cl]_2$	DPEPhos	TMP	120	50 (45)
2	$RhCl_3$	DPEPhos	TMP	120	40 (40)
3	$Rh(OAc)_2$	DPEPhos	TMP	120	42 (50)
4	Rh(IMes)(COD)Cl	DPEPhos	TMP	120	25 (60)
5	$Ir(COD)Cl]_2$	DPEPhos	TMP	120	N.R.
6	$Pd(OAc)_2$	DPEPhos	TMP	120	(4)[c]
7	$NiCl_2$	DPEPhos	TMP	120	N.R.
8	$PtCl_2$	DPEPhos	TMP	120	N.R.
9	$[Rh(COD)Cl]_2$	PPh_3	TMP	120	8 (75)
10	$[Rh(COD)Cl]_2$	dppm	TMP	120	trace (80)
11	$[Rh(COD)Cl]_2$	dppe	TMP	120	4 (95)
12	$[Rh(COD)Cl]_2$	dppp	TMP	120	32 (57)
13	$[Rh(COD)Cl]_2$	dppb	TMP	120	22 (60)
14	$[Rh(COD)Cl]_2$	dppf	TMP	120	29 (34)
15	$[Rh(COD)Cl]_2$	dtbpy	TMP	120	N.R.

16	$[Rh(COD)Cl]_2$	DCyOs	TMP	120	N.R.
17	$[Rh(COD)Cl]_2$	Xantphos	TMP	120	13 (51)
18	$[Rh(COD)Cl]_2$	DPEphos	DIPEA	120	3 (77)
19	$[Rh(COD)Cl]_2$	DPEPhos	Dicyclohexylamine	120	5 (82)
20	$[Rh(COD)Cl]_2$	DPEPhos	DABCO	120	18 (70)
21	$[Rh(COD)Cl]_2$	DPEPhos	PMP	120	26 (58)
22	$[Rh(COD)Cl]_2$	DPEPhos	TBD	120	(62)
23	$[Rh(COD)Cl]_2$	DPEPhos	NaOtBu	120	(99)
24	$[Rh(COD)Cl]_2$	DPEPhos	TMP	70	trace
25	$[Rh(COD)Cl]_2$	DPEPhos	TMP	100	6 (19)

[a] GC yield with 1,3,5-trimethyl as an internal standard [b] Yield of anisole are in parenthesis
[c] Decomposed product was obtained.

Table 5.2. Screening additives



1a **2a** **4aa** **4a'**

entry	Additive	**4aa**[a]	**4a'**[a]	**1a**[a]
1	p-benzoquinone	trace		
2	1-dodecene	48	44	
3	nitrosobenzene			78
4	pinacolone	18	70	
5	triphenylsilane		60	
6	$Cu(OAc)_2$		99	
7	Oxone			57
8	TEMPO	trace	58	
9	BHT[b]	32	58	
10	hydroquinone	trace	61	
11	O_2 (1atm)		80	
12	Mn(0) powder	10	90	

[a] GC yield with 1,3,5-trimethylbenzene as an internal standard
[b] 2,6-Di-*tert*-butyl-4-methylphenol

When we added *p*-benzoquienone as a hydride acceptor (entry 1), the reaction gave a trace amount of the product. In particular, $Cu(OAc)_2$ (entry 6) led to isolation of 99% yield of the reduction product. Eventually, attempts to use a variety of additive were not successful. After discussion with the advisor, time-scale experiments under the standard reaction conditions were carried out (Figure 5.1). The reduction product (anisole) was detected 30 min. after the start of the reaction. Anisole and the product were gradually increased after 30 min. Thus, we provisionally stopped screening the carbonylation of aryl iodides with alcohol.

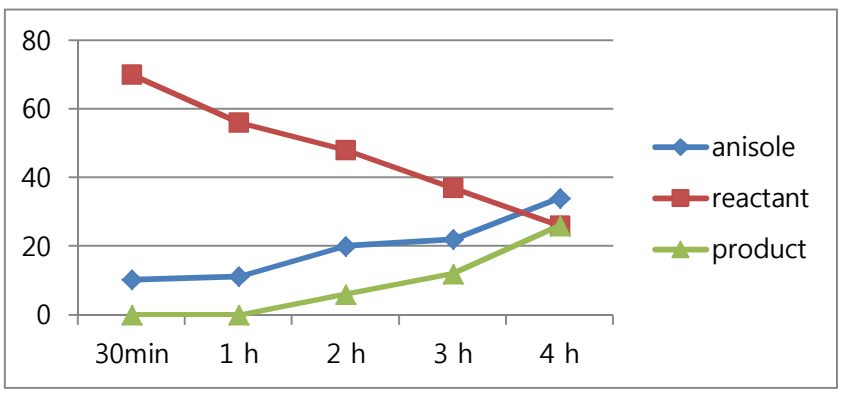
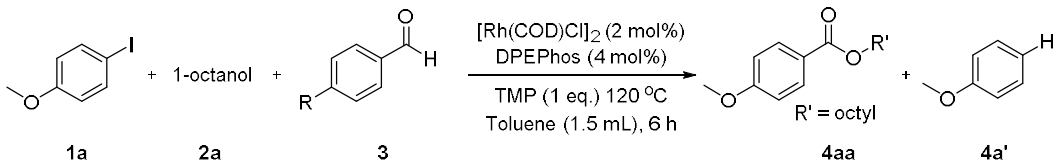


Figure 5.1. Time-Scale experiment

As mentioned above in Introduction section **5.1**, many researchera reported that external CO gas was no longer needed in carbonylation reaction by using a CO surrogate.[4,5,6] Among them, aldehydes, as an additional carbon monoxide source, were attracted our attention. Aldehydes were derived from an oxidation of alcohols. Thus, an aldehyde was added to improve the product yield via enhancement of the decarbonylation step.

Table 5.3. Screening reaction conditions with aldehyde



1a 2a 3 4aa 4a'

entry	cat	Ligand	Base	R	Yield (%)[a,b]
1	$Rh(COD)Cl]_2$	DPEPhos	TMP	Me	90 (10)
2	$RhCl_3$	DPEPhos	TMP	Me	7 (2)
3	$Rh(OAc)_2$	DPEPhos	TMP	Me	75 (17)
4	$[Rh(COD)Cl]_2$ (4 mol%)	DPEPhos	TMP	Me	51 (18)
5	$Ir(COD)Cl]_2$	DPEPhos	TMP	Me	N.R.
6	$Pd(OAc)_2$	DPEPhos	TMP	Me	N.R.
7	$NiCl_2$	DPEPhos	TMP	Me	N.R.
8	$Rh(COD)Cl]_2$	PPh_3	TMP	Me	7 (46)
9	$[Rh(COD)Cl]_2$	dppm	TMP	Me	trace (67)
10	$[Rh(COD)Cl]_2$	dppe	TMP	Me	3 (54)
11	$[Rh(COD)Cl]_2$	dppb	TMP	Me	58 (39)
12	$[Rh(COD)Cl]_2$	dpppent	TMP	Me	49 (31)
13	$[Rh(COD)Cl]_2$	BINAP	TMP	Me	52 (13)
14	$[Rh(COD)Cl]_2$	DPEPhos	TMP	Cl	75 (5)
15	$[Rh(COD)Cl]_2$	DPEPhos	TMP	Br	45 (12)
16	$[Rh(COD)Cl]_2$	DPEPhos	TMP	NO_2	70 (4)
17	$[Rh(COD)Cl]_2$	DPEPhos	TMP	dodecyl aldehyde	73 (19)
18	$[Rh(COD)Cl]_2$	DPEPhos	TMP	propionaldehyde	2 (24)
19	$[Rh(COD)Cl]_2$	DPEPhos	DIPEA	Me	27 (56)
20	$[Rh(COD)Cl]_2$	DPEPhos	DABCO	Me	10 (32)
21	$[Rh(COD)Cl]_2$	DPEPhos	K_2CO_3	Me	37 (2)

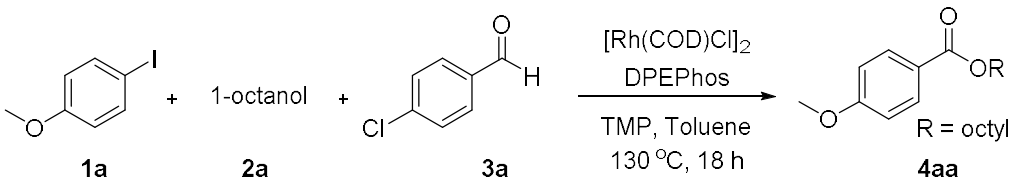
[a] GC yield using 1,3,5-trimethylbenzene as an internal standard.
[b] Reduction product yield are in parenthesis.
[c] Decomposed product was observed.

We studied various metal and rhodium sources (entries 1-7). $[Rh(COD)Cl]_2$ was best catalyst in carbonylation reaction with aldehyde. Other transition metal gave no product. 4 mol % of catalyst diminished the yield of product (entry 4). Next, we tested a series of phosphine ligand (entries 8-13). As expected, monodentate phosphine and bidentate phosphine ligand with small bite angle (entries 8-9) gave trace of product. There is nothing better than DPEPhos ligand in aspects of the yield of product. benzaldehyde with p-chloro functional group gave best yield of the product. In the case of the dodecyl aldehyde, the ester and anisole were isolated in 73% and 19% yields, respectively (entry 17). Other bases such as DIPEA, DABCO and K_2CO_3 are inferior to this catalytic reaction.

We therefore concluded that the addition of an aldehyde aided the formation of rhodium-carbonyl intermediate, and increased the rate of the reaction between the intermediate and the alkoxide to afford the ester. No product was formed in the absence of the alcohol or the rhodium catalyst.

To examine the role of the aldehyde in the alkoxycarbonylation of the aryl iodide more closely, we studied the relation between the yield of the reaction and the ratio of 1-octanol to 4-chlorobenzaldehyde (Table 5.4).

Table 5.4. Yield dependence upon the ratio of 1-octanol to 4-chlorobenzaldehyde[a]



1a **2a** **3a** **4aa**

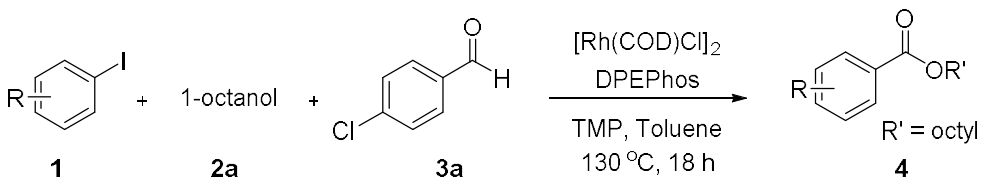
Entry	Alcohol (x eq.)	Aldehyde (y eq.)	Yield[b] (%)
1	1	0	28
2	2	0	44
3	3	0	44
4	0	1	N.R.
5	1	0.7	56
6	1	1	76
7	1	1.3	72
8	1.3	1.3	82
9	2	2	80

[a] Reaction conditions: 0.5 mmol of **1a,** 2 mol% of $Rh(COD)Cl]_2$, 4 mol% of DPEPhos, 1 equiv. of TMP, x equiv. of **2a,** y equiv. of **3a** and 1.5 mL of toluene. [b] Isolated yield.

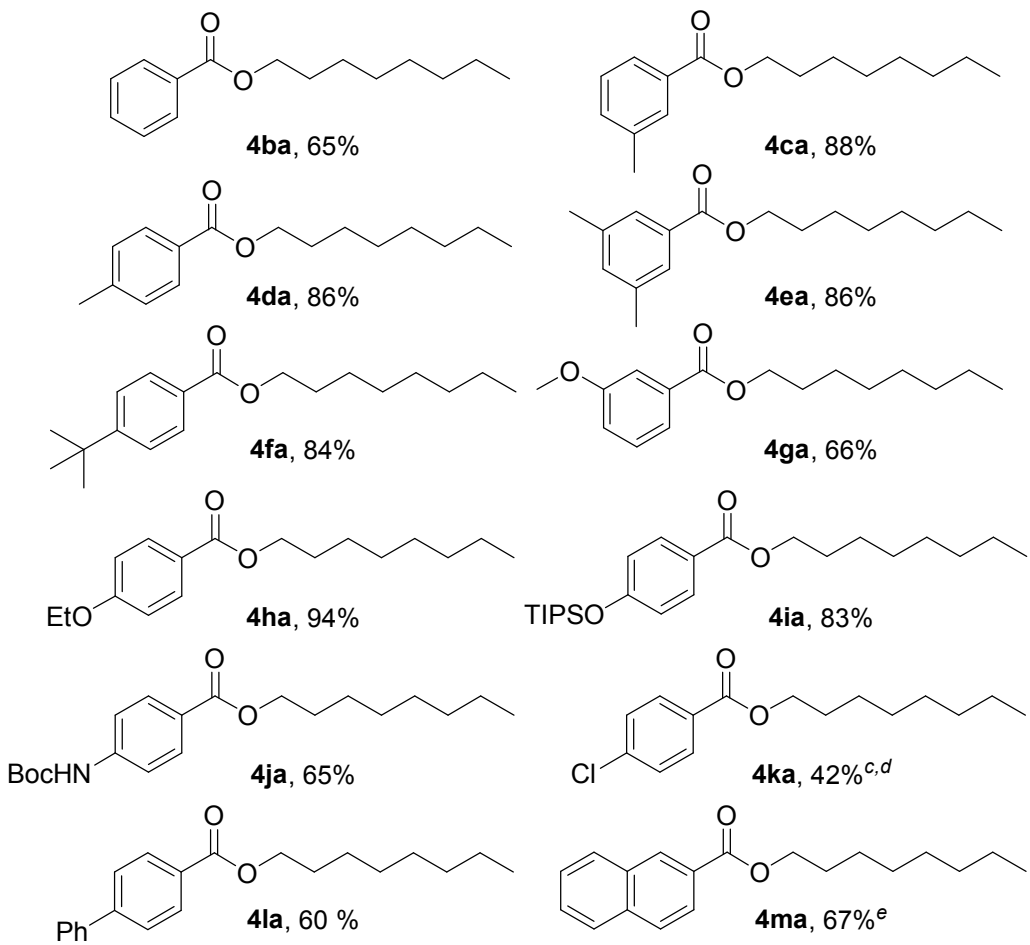
In the presence of 1 equiv. octanol, the expected ester was isolated in 28% yield (entry 1). As the amount of octanol was increased to 2 equiv, the yield also increased to 44% (entry 2). Following this, an additional increase in octanol did not lead to a further increase in yield (entry 3). As expected, no reaction was observed in the absence of octanol (entry 4). When 1.0 equiv octanol and 0.7 equiv 4-chlorobenzaldehyde were used, the yield increased to 56% (entry 5). When equal amounts (1.0 equiv) of octanol and 4-chlorobenzaldehyde were employed, the yield increased to 76% (entry 6). A further increase in aldehyde to 1.2 equiv, with 1.0 equiv octanol, led to a slight decrease in yield (entry 7, 72%). The highest yield (82%) was observed when 1.3 equiv of both octanol and 4-chlorobenzaldehyde were used (entry 8). When 2.0 equiv of both octanol and 4-chlorobenzaldehyde were employed, the yield decreased slightly to 80% (entry 9). This observation suggests that the presence of an aldehyde aids the alkoxycarbonation reaction of the aryl iodide in the presence of an alcohol. From these results, the optimum conditions were established as follows: 0.5 mmol of aryl iodide, 2 mol% of $[Rh(cod)Cl]_2$, 4 mol% of DPEPhos, 1.3 equiv 4-chlorobenzaldehyde, 1.3 equiv octanol, 1 equiv TMP, and 1.5 mL of toluene, at 130 ^{o}C, for 18 h.

5.2.2. Substrate Scope

Table 5.5. Esters from aryl iodides and 1-octanol[a,b]



1 **2a** **3a** **4**



[a] Reaction conditions: 0.5 mmol of **1**, 2 mol% of $Rh(COD)Cl]_2$, 4 mol% of DPEPhos, 1 equiv. of TMP, 1.3 equiv. of **2a**, 1.3 equiv. of **3a** and 1.5 mL of toluene.
[b] Isolated yield. [c] p-tolualdehyde used instead of p-chlorobenzaldehyde.
[d] Some octyl ester impurities. [e] dppp (1,3-bis(diphenylphosphino)propane) as a ligand

With the optimum reaction conditions in hands, the substrate scope was studied next (Table 5.5).

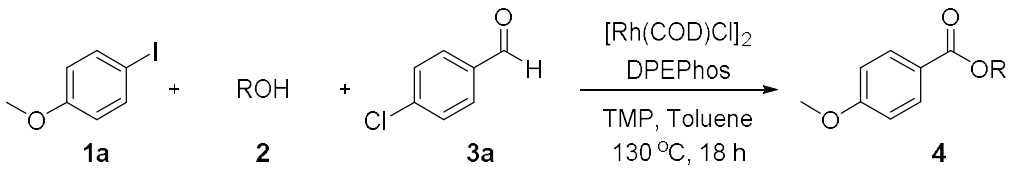
Aryl halides with an electron-donating group were found to be good substrates (**4ba–4ha**). The highest yield (94%) was observed for the substrate with an ether group. In the cases of substrates having an electron-accepting group (**4ka-4la**), the yields were rather low, and in some cases no reaction was observed. An aryl halide bearing a chloro group afforded the corresponding product in < 50% (**4ka**). Moreover, < 60% of the expected product was isolated when 4-iodo-1,1′-biphenyl was used (**4la**). No reaction was observed for aryl iodides having an ester or formyl group. Aryl iodides bearing a hydroxy or amine group did not afford expected product, presumably due to a reaction the rhodium catalyst. However, when the functional groups were blocked, the expected products were isolated in reasonable yields (**4ia-4ja**). Steric effects were observed in some cases; when a methyl group was located at the meta- or para-position, the corresponding ester was isolated in high yields (**4ca-4da**). However, in the case of 1-iodo-2-methylbenzene, no reaction was observed. Similarly, 1-iodonaphthalene did not afford any products in the presence of the ligand DPEPhos. However, when this ligand was substituted with dppp, 67% of the expected product was isolated (**4ma**).

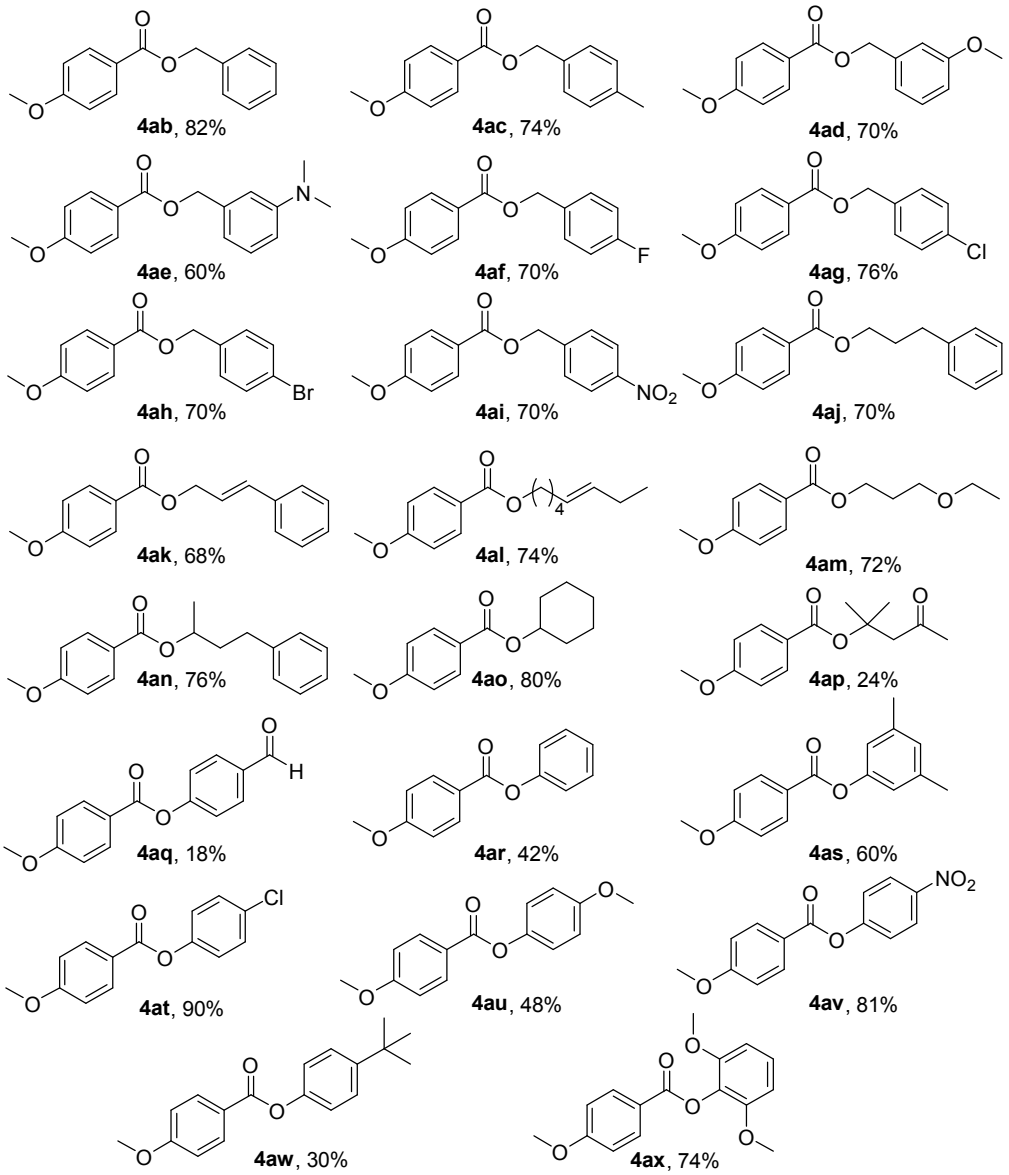
Next, we examined the reaction of the aryl iodide with other alcohols (Table 5.6). Primary alcohols were studied first. Benzyl alcohols bearing electron-donating (Me, OMe, NMe_2) or electron-withdrawing (F, Cl, Br, NO_2) functional groups were found to be good substrates (**4ab-4ai**), and high yields (60 – 82%) were observed. Lengthening the chain between the phenyl and hydroxyl groups to three carbons did not have any influence on the yield (**4aj**). An internal double bond survived during the reaction (**4ak-4al**). When (*E*)-3-phenylpropanol or *(E)*-

oct-5-en-1-ol were used as an alcohol, the expected product was isolated in 68% and 74% yields, respectively. In the case of *(E)*-oct-5-en-1-ol, the product was a mixture of regioisomers. Unfortunately, these could not be separated by conventional separation methods. The ether group retained its position during the reaction (**4am**). For secondary alcohols, including 4-phenylbutanol and cyclohexanol, high yields (76% and 80%, respectively) were observed (**4an-4ao**, respectively). However, the tertiary alcohol 4-hydroxy-4methylpentan-2-one afforded a poor yield (24%) (**4ap**).

When the alcohol used was 4-(hydroxymethyl)phenol, a phenol that bears two kinds of hydroxyl groups, the product (4-Formylphenyl 4-methoxybenzoate)[10] was isolated in 18% yield (**4aq**). The phenyl hydroxyl group was more reactive than the benzyl hydroxyl group. In the phenoxycarbonylation reaction, the aldehyde acted as the sole source of carbon monoxide. This observation prompted us to study the phenoxycarbonylation of other phenols under the same reaction conditions. Seven more phenols were tested as substrates (**4ar-4ax**). The corresponding products were isolated in the reasonable to high yields (42-88%). Electron-deficient phenols are more reactive than electron-rich phenols. Thus, phenols, that are less reactive in the carbonylation reaction,[11] are suitable reaction partners in the catalytic reaction. Phenyl esters could therefore serve as useful acylating reagents for the production of other carboxylate derivatives.[12]

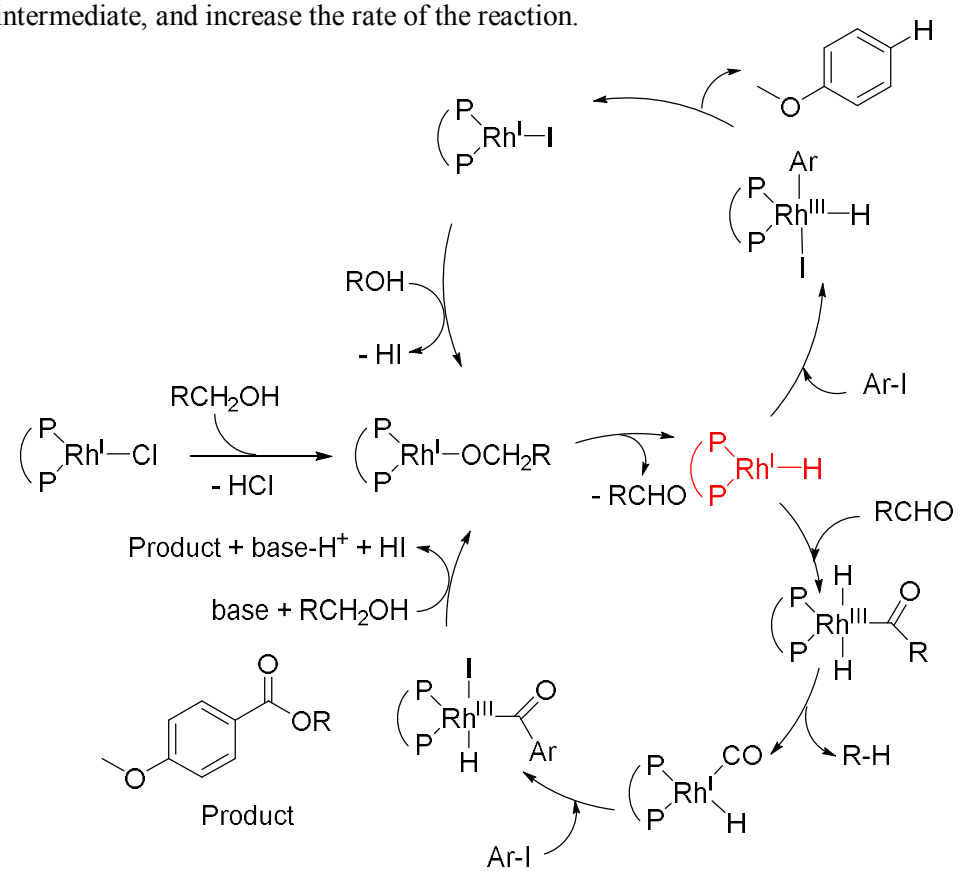
Table 5.6. Esters from aryl iodides and various alcohols[a,b]





[a] Reaction conditions: 0.5 mmol of **1a**, 2 mol% of $Rh(COD)Cl]_2$, 4 mol% of DPEPhos, 1 equiv. of TMP, 1.3 equiv. of **2**, 1.3 equiv. of **3a** and 1.5 mL of toluene. [b] Isolated yield.

On the basis of the experimental results, together with previously studies,[8,9,13] a plausible reaction mechanism can be drawn for the alkoxycarbonylation of an aryl halide, in the presence of a rhodium compound, with an alcohol and aldehyde (Scheme 5.3 and SI). Two catalytic cycles may be operated under our reaction conditions, namely, a reduction path via a rhodium-hydride intermediate, and an alkoxycarbonylation through a rhodium-carbonyl intermediate. The rhodium-carbonyl intermediate reacts with the aryl iodide in the presence of an alkoxide, leading to the formation of an ester. The rhodium-hydride intermediate reacts with the aryl halide to afford the reduced product as a minor pathway. We predict that the addition of an aldehyde would aid the formation of the rhodium-carbonyl intermediate, and increase the rate of the reaction.



Scheme 5.3. Proposed reaction mechanism

5.3. Conclusion

In this chapter, we have developed a CO-gas-free alkoxycarbonylation of aryl iodide in the presence of an $[Rh(COD)Cl]_2$/DPEPhos catalytic system and an alcohol with/without an aldehyde. Without the aldehyde, the alcohol acted as both a CO and a nucleophile source to afford the alkoxycarbonylated product in moderate yield. In the presence of both the alcohol and aldehyde, high yields of the alkoxycarbonylated product were isolated. This occurred because the aldehyde assisted the carbonylation reaction. When phenols were used instead of alcohols, phenoxycarbonylation products were also isolated in high yields. Thus, simple aldehydes and primary alcohols could be converted to a useful CO source without any additives. The results will expand the field of carbonylation reactions.

5.4. Experimental Section

Materials

All solvents were dried and distilled according to standard methods before use. Solvents utilized in this work were obtained from Sigma-Aldrich and Samchun Pure Chemicals (hexanes, ethyl acetate, diethyl ether, dichloromethane, and acetone). Toluene were dried over Na and distilled under nitrogen. *n*-Hexane, diethyl ether, and ethyl acetate were used without further purification. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, or TCI and were used as received. $[Rh(COD)Cl]_2$ were purchased from Pressure Chem. DPEPhos((oxybis(2,1-phenylene))bis(diphenylphosphane)) were purchased from Alfa Aesar. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254). The TLC plates were visualized by UV-light (254 nm) and treatment with acidic *p*-anisaldehyde and $KMnO_4$ stain followed by gentle heating. Workup procedures were done in air. Flash column chromatography was carried out on Merck 60 silica gel (230 – 400 mesh).

Characterization

^1H and ^{13}C NMR spectra were recorded with Agilent 400-MR DD2 (400 MHz and 100 MHz, respectively) spectrometer. ^1H NMR spectra were taken in $CDCl_3$ and were referenced to residual TMS (7.26 ppm) and reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.00 ppm). High-Resolution Mass Spectra were obtained at the Korea Basic Science Institute (Daegu, South Korea) on a Jeol JMS 700 high resolution mass spectrometer. GC-MS analyses were performed with a HP-6890 series with a HP-5 capillary column (30 m x 0.25 mm; coating thickness 0.25 μm) and Agilent 5973 Network Mass Selective detector. Analytical condition – initial temperature:

50 ^{o}C, raising temperature 10 ^{o}C / min, final temperature: 280 ^{o}C, He gas, Pressure: 7.56 psi, Total flow: 53.7 mL / min.

Synthesis

Procedure for the entries reported Table 5.1 to 5.2 from aryl iodide and alcohol

Reactions were performed in a schlenk tube equipped with a stirring bar and capped with a rubber septum. The followings were placed in the tube in order: 2 mol% of catalyst, 4 mol% of ligand, 0.5 mmol of aryl iodide, 1 equiv. of base, 3 equiv of 1-octanol and 1.5 mL of toluene. The mixture was stirred at 120 ^{o}C for 18 h. The concentrated reaction mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate) to afford the product.

Procedure for the entries reported Table 5.5 to 5.6 from aryl iodide and alcohol

Reactions were performed in a schlenk tube equipped with a stirring bar and capped with a rubber septum. The followings were placed in the tube in order: 2 mol% of catalyst, 4 mol% of ligand, 0.5 mmol of aryl iodide, 1 equiv. of base, 1.3 equiv. of aldehyde, 1.3 equiv of alcohol and 1.5 mL of toluene. The mixture was stirred at 130 ^{o}C for 18 h. The concentrated reaction mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate) to afford the product.

4ba: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.3 Hz, 2 H), 7.47 (t, J = 7.4 Hz, 1 H), 7.36 (t, J = 7.7 Hz, 2 H), 4.24 (t, J = 6.7 Hz, 2 H), 1.83 – 1.59 (m, 2 H), 1.57 – 1.32 (m, 2 H), 1.24 (m, 8 H), 0.81 (t, J = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 132.7, 130.5, 129.5, 128.3, 65.1, 31.7, 29.2, 29.1, 28.7, 26.0, 22.6, 14.1. IR (ν_{CO}): 1723 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{22}O_2, M]^+$ 234.1620, found 234.1620

4ca: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.7 Hz, 2 H), 7.25 (m, 2 H), 4.23 (t, *J* = 6.7 Hz, 2 H), 2.32 (s, 3 H), 1.72 – 1.65 (m, 2 H), 1.40 – 1.33 (m, 2 H), 1.28 – 1.19 (m, 8 H), 0.81 (t, *J* = 6.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 138.0, 133.5, 130.4, 130.0, 128.2, 126.6, 65.1, 31.8, 29.22, 29.16, 28.7, 26.0, 22.6, 21.2, 14.1. IR (ν_{CO}): 1721 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{24}O_2, M]^+$ 248.1776, found 248.1777

4da: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 2 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 4.22 (t, *J* = 6.7 Hz, 2 H), 2.33 (s, 3 H), 1.72 – 1.63 (m, 2 H), 1.41 – 1.32 (m, 2 H), 1.24 (m, 8 H), 0.81 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 143.4, 129.5, 129.0, 127.8, 64.9, 31.8, 29.23, 29.17, 28.7, 26.0, 22.6, 21.6, 14.1. IR (ν_{CO}): 1721 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{24}O_2, M]^+$ 248.1776, found 248.1777

4ea: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 2 H), 7.09 (s, 1 H), 4.21 (t, *J* = 6.7 Hz, 2 H), 2.27 (s, 6 H), 1.71 – 1.65 (m, 2 H), 1.39 – 1.32 (m, 2H), 1.27 – 1.16 (m, 8 H), 0.80 (t, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 137.9, 134.4, 130.4, 127.2, 65.0, 31.8, 29.23, 29.16, 28.7, 26.0, 22.6, 21.1, 14.1. IR (ν_{CO}): 1719 cm^{-1}, HRMS (EI) calc. for $[C_{17}H_{26}O_2, M]^+$ 262.1933, found 262.1933

4fa: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 4.22 (t, *J* = 6.6 Hz, 2 H), 1.68 (dd, *J* = 14.2, 7.1 Hz, 2 H), 1.39 – 1.32 (m, 2 H), 1.26 (s, 9 H), 1.29 – 1.22 (m, 8 H), 0.81 (t, *J* = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 156.4, 129.4, 127.7, 125.2, 64.9, 35.0, 31.8, 31.1, 29.23, 29.18, 28.7, 26.0, 22.6, 14.1. IR (ν_{CO}): 1721 cm^{-1}, HRMS (EI) calc. for $[C_{19}H_{30}O_2, M]^+$ 290.2246, found 290.2246

4ga: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 1 H), 7.49 (s, 1 H), 7.26 (t, *J* = 8.4 Hz, 1 H), 7.01 (d, *J* = 8.2 Hz, 1 H), 4.23 (t, *J* = 7.3 Hz, 2 H), 3.77 (s, 3 H), 1.72 – 1.65 (m, 2 H), 1.35 (m, 2 H), 1.22 (m, 8 H), 0.80 (t, *J* = 5.0 Hz, 3 H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 166.5, 159.5, 131.8, 129.4, 121.9, 119.2, 114.0, 65.2, 55.4, 31.8, 29.21, 29.16, 28.7, 26.0, 22.6, 14.1. IR (ν_{CO}): 1700 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{24}O_2, M]^+$ 264.1725, found 264.1727

4ha: ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 4.18 (t, *J* = 6.6 Hz, 2 H), 3.96 (q, *J* = 6.9 Hz, 2 H), 1.68 – 1.61 (m, 2 H), 1.34 – 1.30(m, 5 H), 1.28 – 1.12 (m, 8 H), 0.79 (t, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 162.5, 131.4, 122.6, 113.8, 64.7, 63.5, 31.7, 29.17, 29.11, 28.7, 26.0, 22.5, 14.5, 14.0. IR (ν_{CO}): 1717 cm^{-1}, HRMS (EI) calc. for $[C_{17}H_{26}O_3, M]^+$ 278.1882, found 278.1884

4ia: ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.9 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 4.20 (t, *J* = 6.7 Hz, 2 H), 1.71 – 1.63 (m, 2H), 1.40 – 1.32 (m, 2H), 1.23 (m, 10 H), 1.04 (s, 9 H), 1.02 (s, 7 H), 0.81 (t, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 160.3, 131.5, 123.3, 119.6, 64.8, 31.8, 29.26, 29.20, 28.8, 26.1, 22.6, 17.9, 14.1, 12.7. IR (ν_{CO}): 1705 cm^{-1}, HRMS (EI) calc. for $[C_{24}H_{42}O_3Si, M]^+$ 406.2903, found 406.2906

4ja: ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 6.86 (s, 1 H), 4.21 (t, *J* = 6.6 Hz, 2 H), 1.70 – 1.63 (m, 2 H), 1.43 (s, 9 H), 1.37 – 1.33 (m, 2 H), 1.23 – 1.20 (m, 8 H), 0.79 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 152.2, 142.7, 130.8, 124.6, 117.3, 81.0, 64.9, 31.7, 29.19, 29.13, 28.7, 28.2, 26.0, 22.6, 14.0. IR (ν_{CO}): 1704 cm^{-1}, HRMS (EI) calc. for $[C_{20}H_{31}O_4N, M]^+$ 349.2253, found 349.2255

4ka: with octyl ester impurities, ^1H NMR (400 MHz, $cdcl_3$) δ 7.90 (d, *J* = 8.2 Hz, 2 H), 7.33 (d, *J* = 8.5 Hz, 2 H), 4.23 (t, *J* = 6.7 Hz, 2 H), 1.72 – 1.64 (m, 2 H), 1.38 – 1.32 (m, 2 H), 1.23 – 1.20 (m, 8 H), 0.81 (t, *J* = 4.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 139.2, 130.9, 128.9, 128.6, 65.4, 31.8, 29.20, 29.15, 28.6, 26.0,

22.6, 14.1. IR (ν_{CO}): 1700 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{21}O_2Cl, M]^+$ 268.1230, found 268.1233

4la: ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 2 H), 7.57 (dd, *J* = 13.8, 7.8 Hz, 4 H), 7.40 (t, *J* = 7.4 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 4.27 (t, *J* = 6.6 Hz, 2 H), 1.76 – 1.67 (m, 2 H), 1.42 – 1.35 (m, 2 H), 1.31 – 1.18 (m, 8 H), 0.82 (t, *J* = 6.3 Hz, 3 H). ^{13}C NMR (100 MHz, $cdcl_3$) δ 166.6, 145.5, 140.1, 130.0, 129.3, 128.9, 128.1, 127.3, 127.0, 65.2, 31.8, 29.26, 29.20, 28.8, 26.1, 22.6, 14.1. IR (ν_{CO}): 1720 cm^{-1}, HRMS (EI) calc. for $[C_{21}H_{26}O_2, M]^+$ 310.1933, found 310.1934

4ma: ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 8.6 Hz, 1 H), 8.08 (d, *J* = 6.9 Hz, 1 H), 7.90 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 8.1 Hz, 1), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.41 (dt, *J* = 14.1, 7.6 Hz, 2 H), 4.32 (t, *J* = 6.6 Hz, 2 H), 1.78 – 1.68 (m, 2 H), 1.42 – 1.35 (m, 2 H), 1.31 – 1.15 (m, 8 H), 0.80 (t, *J* = 5.8 Hz, 3 H). ^{13}C NMR (100 MHz, $cdcl_3$) δ 167.6, 133.8, 133.1, 131.3, 130.0, 128.4, 127.6, 127.4, 126.1, 125.8, 124.4, 65.2, 31.7, 29.20, 29.15, 28.7, 26.1, 22.6, 14.0. IR (ν_{CO}): 1716 cm^{-1}, HRMS (EI) calc. for $[C_{19}H_{24}O_2, M]^+$ 284.1776, found 284.1779

4ab: ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 7.2 Hz, 2 H), 7.33 – 7.22 (m, 3 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 5.26 (s, 2 H), 3.77 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.4, 136.3, 131.7, 128.5, 128.10, 128.06, 122.5, 113.6, 66.4, 55.4. IR (ν_{CO}): 1715 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{14}O_3, M]^+$ 242.0943, found 242.0941

4ac: ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 7.7 Hz, 2 H), 7.08 (d, *J* = 7.6 Hz, 2 H), 6.79 (d, *J* = 8.3 Hz, 2 H), 5.19 (s, 2 H), 3.72 (s, 3 H), 2.25 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.3, 137.9, 133.2, 131.6, 129.1, 128.2, 122.6, 113.5, 66.3, 55.4, 21.1. IR (ν_{CO}): 1708 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{16}O_3, M]^+$ 256.1099, found 256.1102, m.p. 38.4 ^oC

4ad: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.7 Hz, 2 H), 7.20 (t, *J* = 7.9 Hz, 1 H), 6.98 – 6.85 (m, 2 H), 6.85 – 6.71 (m, 3 H), 5.21 (s, 2 H), 3.74 (s, 3 H), 3.71 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 163.4, 159.7, 137.8, 131.7, 129.5, 122.4, 120.2, 113.6, 113.5, 113.6, 66.2, 55.3, 55.2. IR (ν_{CO}): 1712 cm^{-1}, HRMS (EI) calc. for $[C_{16}H_{16}O_4, M]^+$ 272.1049, found 272.1051

4ae: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2 H), 7.15 (t, *J* = 7.8 Hz, 1 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 6.70 (d, *J* = 7.8 Hz, 2 H), 6.60 (d, *J* = 8.5 Hz, 1 H), 5.19 (s, 2 H), 3.73 (s, 3 H), 2.85 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.3, 150.7, 137.0, 131.7, 129.2, 122.6, 116.2, 113.5, 112.2, 112.1, 67.0, 55.3, 40.5. IR (ν_{CO}): 1709 cm^{-1}, HRMS (EI) calc. for $[C_{17}H_{19}O_3N, M]^+$ 285.1365, found 285.1366

4af: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2 H), 7.31 (dd, *J* = 8.5, 5.5 Hz, 2 H), 6.96 (t, *J* = 8.7 Hz, 2 H), 6.81 (d, *J* = 8.9 Hz, 2 H), 5.19 (s, 2 H), 3.74 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 163.8, 163.4, 161.3, 132.11, 132.08, 131.7, 130.9, 130.02, 122.4, 115.5, 115.3, 113.6, 65.6, 55.4. IR (ν_{CO}): 1711 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{13}O_3F, M]^+$ 260.0849, found 260.0850, m.p.: 54 ^{o}C

4ag: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2 H), 7.24 (q, *J* = 8.6 Hz, 4 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 5.18 (s, 2 H), 3.73 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.4, 134.7, 133.9, 131.6, 129.4, 128.6, 122.2, 113.6, 65.4, 55.3. IR (ν_{CO}): 1712 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{13}O_3Cl, M]^+$ 276.0553, found 276.0552, m.p. : 86 ^{o}C

4ah: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2 H), 7.39 (d, *J* = 8.3 Hz, 2 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 6.81 (d, *J* = 8.9 Hz, 2 H), 5.17 (s, 2 H), 3.74 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.4, 135.3, 131.64, 131.61, 129.7, 122.2, 122.1, 113.6, 65.5, 55.3. IR (ν_{CO}): 1713 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{13}O_3Br,$

M]$^+$ 320.0048, found 320.0049, m.p. : 94 ^{o}C

4ai: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 2 H), 7.94 (d, *J* = 8.6 Hz, 2 H), 7.49 (d, *J* = 8.3 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 5.33 (s, 2 H), 3.76 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 163.6, 147.5, 143.6, 131.7, 128.1, 123.7, 121.7, 113.7, 64.8, 55.4. IR (ν_{CO}): 1714 cm^{-1}, HRMS (EI) calc. for [$C_{15}H_{13}O_5N$, M]$^+$ 287.0794, found 287.0795, m.p. : 132 ^{o}C

4aj: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2 H), 7.17 (d, *J* = 7.0 Hz, 2 H), 7.10 (d, *J* = 6.5 Hz, 3 H), 6.80 (d, *J* = 8.2 Hz, 2 H), 4.20 (t, *J* = 6.1 Hz, 2 H), 3.72 (s, 3 H), 2.67 (t, *J* = 7.4 Hz, 2 H), 1.98 (t, *J* = 5.2 Hz 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 163.2, 141.2, 131.6, 131.5, 128.3, 125.9, 122.7, 113.5, 63.9, 55.3, 32.2, 30.3. IR (ν_{CO}): 1716 cm^{-1}, HRMS (EI) calc. for [$C_{17}H_{18}O_3$, M]$^+$ 270.1256, found 270.1253

4ak: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.6 Hz, 2 H), 7.30 (d, *J* = 7.5 Hz, 2 H), 7.21 (t, *J* = 7.4 Hz, 2 H), 7.15 (d, *J* = 7.0 Hz, 1 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 6.62 (d, *J* = 15.9 Hz, 1 H), 6.29 (dt, *J* = 13.1, 6.3 Hz, 1 H), 4.84 (d, *J* = 6.2 Hz, 2 H), 3.72 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 163.3, 136.2, 133.9, 131.6, 128.5, 127.9, 126.5, 123.5, 122.5, 113.5, 65.1, 55.3. IR (ν_{CO}): 1709 cm^{-1}, HRMS (EI) calc. for [$C_{17}H_{16}O_3$, M]$^+$ 268.1099 found 268.1097

4al: with regioisomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.3 Hz, 2 H), 5.42 – 5.20 (m, 2 H), 4.20 (t, *J* = 6.5 Hz, 2 H), 3.75 (s, 6 H), 2.04 – 1.92 (m, 4 H), 1.73 – 1.63 (m, 2 H), 1.45 – 1.37 (m, 2 H), 0.87 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 163.2, 132.1, 131.4, 128.4, 122.8, 113.4, 64.5, 55.3, 28.2, 26.6, 26.1, 20.5, 14.3. IR (ν_{CO}): 1702 cm^{-1}, HRMS (EI) calc. for [$C_{16}H_{22}O_3$, M]$^+$ 262.1569 found 262.1568

4am: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 2 H), 6.81 (d, *J* = 8.1 Hz,

2 H), 4.29 (t, J = 6.0 Hz, 2 H), 3.75 (s, 3 H), 3.47 (t, J = 5.9 Hz, 2 H), 3.40 (d, J = 6.8 Hz, 2 H), 1.98 – 1.90 (m, 2 H), 1.10 (t, J = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 163.2, 131.4, 122.7, 113.4, 67.0, 66.1, 61.8, 55.3, 29.1, 15.0. IR (ν_{CO}): 1713 cm^{-1}, HRMS (EI) calc. for $[C_{13}H_{18}O_4, M]^+$ 238.1205 found 238.1206

4an: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.7 Hz, 2 H), 7.16 (t, J = 7.4 Hz, 2 H), 7.08 (d, J = 7.5 Hz, 3 H), 6.81 (d, J = 8.7 Hz, 2 H), 5.06 (dd, J = 12.4, 6.2 Hz, 1 H), 3.73 (s, 3 H), 2.68 – 2.56 (m, 2 H), 2.02 – 1.94 (m, 1 H), 1.86 – 1.79 (m, 1 H), 1.26 (d, J = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 163.2, 141.5, 131.4, 128.3, 128.2, 125.8, 123.1, 113.5, 70.7, 55.3, 37.7, 31.8, 20.1. IR (ν_{CO}): 1700 cm^{-1}, HRMS (EI) calc. for $[C_{18}H_{20}O_3, M]^+$ 284.1412 found 284.1414

4ao: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.7 Hz, 2 H), 6.81 (d, J = 8.7 Hz, 2 H), 4.94 – 4.85 (m, 1 H), 3.74 (s, 3 H), 1.87 – 1.83 (m, 2 H), 1.73 – 1.65 (m, 2 H), 1.53 – 1.44 (m, 3 H), 1.38 – 1.22 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 163.1, 131.4, 123.3, 113.4, 72.5, 55.3, 31.6, 25.4, 23.6. IR (ν_{CO}): 1704 cm^{-1}, HRMS (EI) calc. for $[C_{14}H_{18}O_3, M]^+$ 234.1256 found 234.1258

4ap: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 5.3 Hz, 2 H), 6.82 (d, J = 5.3 Hz, 2 H), 3.77 (s, 3 H), 3.09 (s, 2 H), 2.08 (s, 3 H), 1.57 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 165.6, 163.2, 131.4, 123.8, 113.5, 80.4, 55.4, 52.4, 31.7, 26.6. IR (ν_{CO}): 1703 cm^{-1}, HRMS (EI) calc. for $[C_{14}H_{18}O_4, M]^+$ 250.1205 found 250.1205

4aq: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1 H), 8.08 (d, J = 8.7 Hz, 2 H), 7.88 (d, J = 8.3 Hz, 2 H), 7.32 (d, J = 8.3 Hz, 2 H), 6.92 (d, J = 8.7 Hz, 2 H), 3.83 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 164.2, 164.1, 155.8, 133.9, 132.4, 131.2, 122.6, 121.1, 114.0, 55.5. IR (ν_{CO}): 1724, 1695 cm^{-1}, HRMS (EI) calc. for $[C_{15}H_{12}O_4, M]^+$ 256.0736 found 256.0733

4ar: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.7 Hz, 2 H), 7.32 (t, J = 6.7 Hz, 2

H), 7.18 – 7.09 (m, 3 H), 6.89 (d, *J* = 7.7 Hz, 2 H), 3.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 163.8, 151.0, 132.2, 129.4, 125.6, 121.8, 121.7, 113.8, 55.4; IR (ν_{CO}): 1732 cm^{-1}; HRMS (EI) calc. for $[C_{14}H_{12}O_3, M]^+$ 228.0786 found 228.0782, m.p.: 74 °C

4as: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 6.78 (s, 1 H), 6.72 (s, 2 H), 3.76 (s, 3 H), 2.23 (s, 6 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 163.7, 150.9, 139.1, 132.1, 127.4, 121.9, 119.3, 113.7, 55.4, 21.2; IR (ν_{CO}): 1725 cm^{-1}; HRMS (EI) calc. for $[C_{16}H_{16}O_3, M]^+$ 256.1099 found 256.1103; m.p.: 62 °C

4at ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 5.7 Hz, 2 H), 7.23 (d, *J* = 5.6 Hz, 2 H), 7.02 (d, *J* = 5.6 Hz, 2 H), 6.84 (d, *J* = 5.8 Hz, 2 H), 3.74 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 163.9, 149.4, 132.2, 130.9, 129.3, 123.1, 121.3, 113.8, 55.4; IR (ν_{CO}): 1728 cm^{-1}; HRMS (EI) calc. for $[C_{14}H_{11}O_3Cl, M]^+$ 262.0397 found 262.0400; m.p.: 96 °C

4au: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.6 Hz, 2 H), 7.02 (d, *J* = 8.7 Hz, 2 H), 6.85 (dd, *J* = 16.4, 8.7 Hz, 4 H), 3.77 (s, 3 H), 3.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.7, 157.1, 144.4, 132.1, 122.4, 121.8, 114.4, 113.7, 55.46, 55.40; IR (ν_{CO}): 1728 cm^{-1}; HRMS (EI) calc. for $[C_{15}H_{14}O_4, M]^+$ 258.0892 found 258.0890; m.p.: 124 °C

4av: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.0 Hz, 2 H), 8.07 (d, *J* = 8.8 Hz, 2 H), 7.33 (d, *J* = 9.0 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 3.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 163.9, 155.9, 145.2, 132.5, 125.2, 122.6, 120.7, 114.0, 55.6; IR (ν_{CO}): 1735 cm^{-1}; HRMS (EI) calc. for $[C_{14}H_{11}O_5N, M]^+$ 273.0637 found 273.0639; m.p.: 167 °C

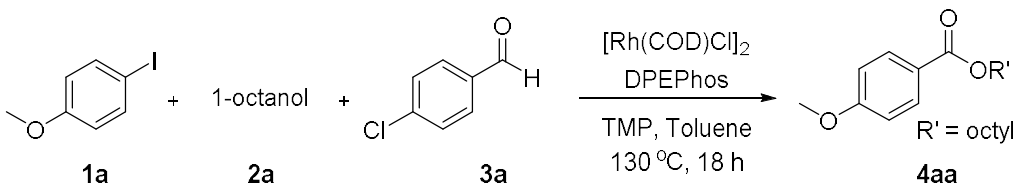
4aw: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.9 Hz, 2 H), 7.34 (d, *J* = 7.6 Hz, 2

H), 7.04 (d, *J* = 7.4 Hz, 2 H), 6.89 (d, *J* = 7.9 Hz, 2 H), 3.79 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 163.8, 148.6, 148.4, 132.2, 126.3, 122.0, 121.0, 113.7, 55.4, 34.4, 31.4; IR (ν_{CO}): 1729 cm^{-1}; HRMS (EI) calc. for [$C_{18}H_{20}O_3$, M]$^+$ 284.1412 found 284.1411; m.p.: 103 ^oC

4ax: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 3H), 3.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 163.6, 152.5, 132.4, 128.9, 126.1, 121.7, 113.6, 104.9, 56.1, 55.4; IR (ν_{CO}): 1734 cm^{-1}; HRMS (EI) calc. for [$C_{16}H_{16}O_5$, M]$^+$ 288.0998 found 288.0999; m.p.: 119 ^oC

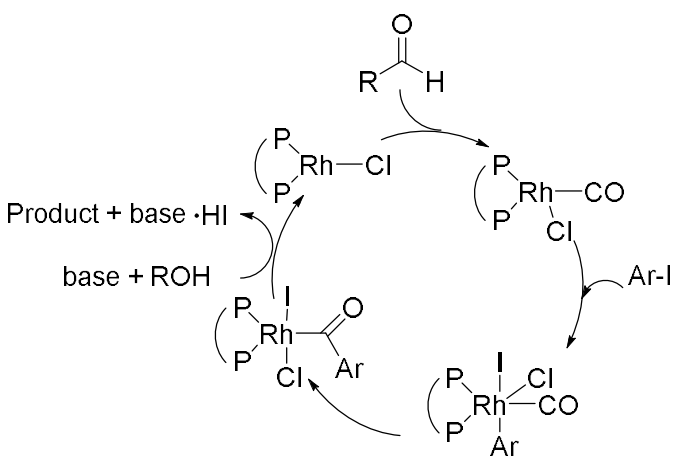
5.5. Supporting Information

Table S5.1. Control experiment for proposed mechanism

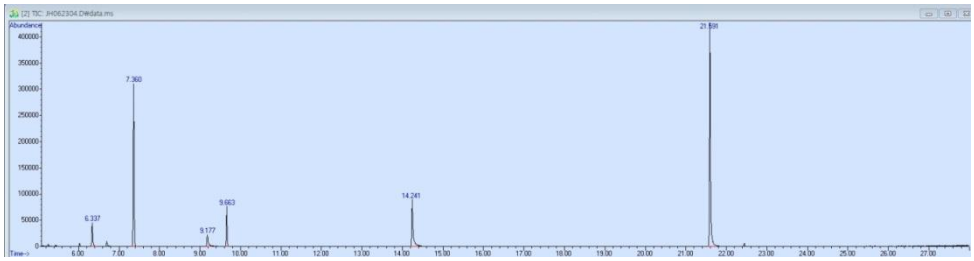


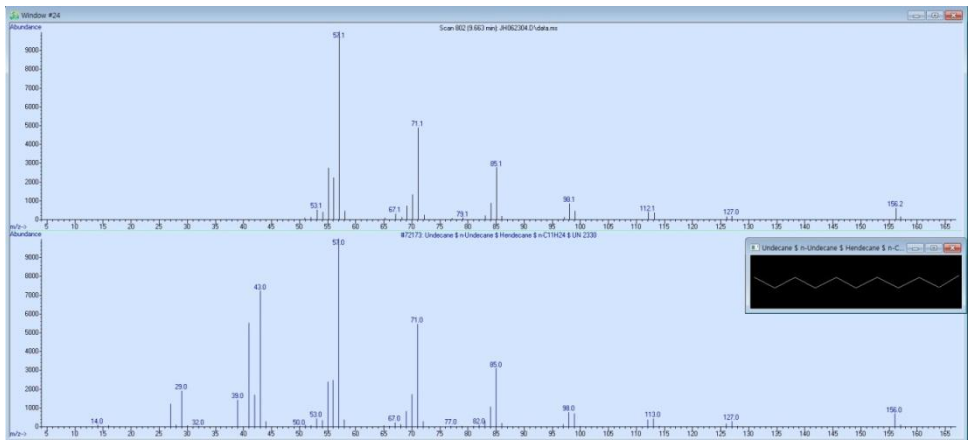
Entry	Variation from standard condition	Yield[b] (%)
1	Without $[Rh(COD)Cl]_2$	trace
2	Without alcohol	No reaction
3	Without ligand	No reaction
4	Without aldehyde	44
5	Without base	No reaction

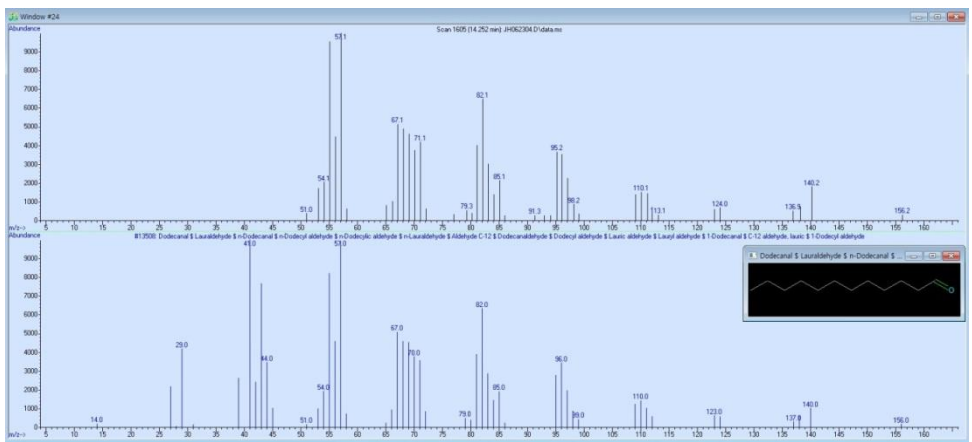
[a] Reaction conditions: 0.5 mmol of **1a**, 2 mol% of $Rh(COD)Cl]_2$, 4 mol% of DPEPhos, 1 equiv. of TMP, 1.3 equiv. of **2a**, 1.3 equiv. of **3a** and 1.5 mL of toluene. [b] Isolated yield.



Scheme S5.1. Proposed mechanism with aldehyde







Retention time – 9.663 min : undecane (R-H moiety)

14.241 min : dodecyl aldehyde (CO surrogate)

21.591 min : product

Figure S5.1. GC data using dodecyl aldehyde as a CO source

5.6. References

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Chapter 6. Rhodium-Catalyzed Intermolecular Carbonylative [2+2+1] Cycloaddition of Alkynes Using Alcohol as the Carbon Monoxide Source for the Formation of Cyclopentenones

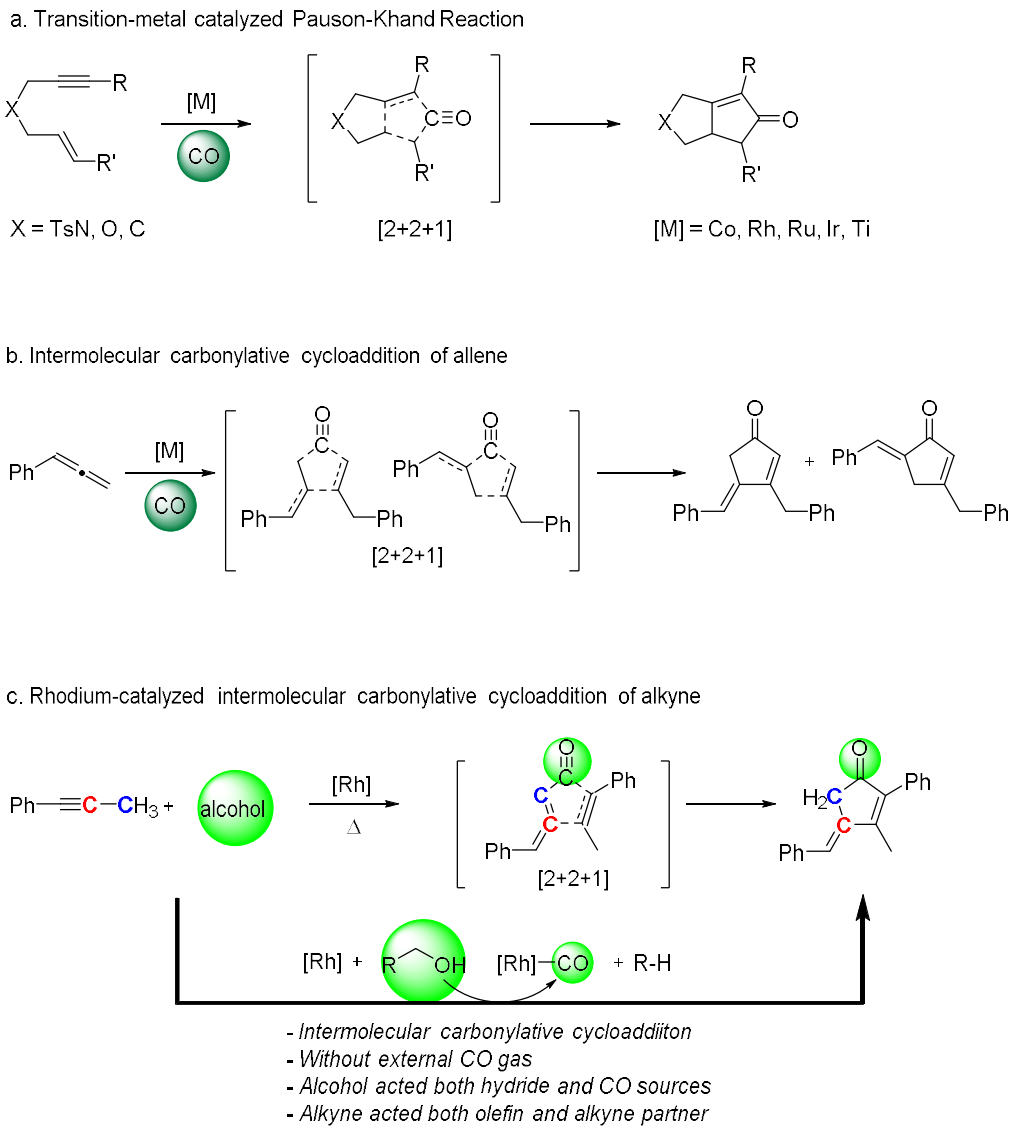
6.1. Introduction

In Chapter 5, we discussed the use of alcohol as a carbon monoxide source. Alcohol acted both CO and nucleophile. Although it was not sufficient to use alcohol as a sole carbon monoxide sources in carbonylation of aryl iodide, the results of Chapter 5 motivated us to expand the chemistry of rhodium/ bidentate phosphine with alcohol system in carbonylation reactions. As a follow-up study of Chapter 5, we focused on the study of the carbonylated cyclized products, e.g. cycopentanones or cyclopentenones.

The cyclopentenone motif is a very powerful synthon for the synthesis of various biologically active molecules.[1] Among the available synthetic methods,[2-4] the Pauson-Khand reaction (PKR) has been developed as a powerful tool in the synthesis of cyclopentenone cores (Scheme 6.1a).[5] In 1994, an important catalytic conversion, using $Co_2(CO)_8$, $P(OPh)_3$, and 3 bar of CO as reagents, was reported.[6] Since then, other metals, including ruthenium,[7] rhodium,[8] iridium,[9] and titanium[10] have been established as suitable catalysts of the PKR. Moreover, synthetic utility has been significantly expanded by the incorporation of more reactive allenes in place of alkenes.[11]

Rhodium-catalyzed carbonylative cycloaddition reactions of unsaturated hydrocarbons have been studied extensively.[11,12] Although considerable progress has been made in this area, the intermolecular version may suffer from regioselectivity, reactivity of substrates, or feasibility of the required catalyst. Thus, development of an efficient synthetic method with regio-controlled, readily available substrates and a proper catalyst is still required. Toward this end, we and other groups reported[13] the carbonylative cycloaddition of allenes with CO in the

presence of a catalyst (Scheme 6.1b). Although the inclusion of allenes within the scope of useful substrates has widened the utility of the rhodium-catalyzed carbonylative cycloaddition, their use[14] leads to regioselectivity problems and undesirable side reactions, such as dimerization and hydrodimerization.[15]



Scheme 6.1. Transition metal-catalyzed formal [2+2+1] cycloaddition

In general, carbonylation reactions, including PK-type reactions, are carried out in the presence of carbon monoxide (Schemes 6.1a and 6.1b). However, the use of CO gas is not desirable due to its toxicity and difficulty to control. Thus, in some studies, CO was replaced by other organic and inorganic carbonyl compounds.[16] Several years ago, we reported the use of alcohols as a source of CO and hydride in a rhodium-catalyzed intramolecular Pauson-Khand reaction without the requirement for external CO gas and reductive cyclization.[17,18] With this in mind, we designed a new, one-pot synthesis including alkyne isomerization followed by intermolecular [2+2+1] carbonylative cycloaddition[19] using an alcohol as a CO surrogate. We hypothesized that the alkyne could act as an allene replacement due to the feasibility of its isomerization with a transition metal hydride, such as rhodium or iridium.[20] Thus, 1-aryl-1-propynes were expected to serve both as an alkene and alkyne-like moiety in the construction of a cyclopentenone skeleton (Scheme 6.1c). We envisioned that it would be a straightforward and efficient process for assembling cyclopentenones from readily available 1-aryl-1-propynes[21,22] and alcohols. To the best of our knowledge, this is the first report of rhodium-catalyzed intermolecular carbonylative cycloaddition of alkynes with alcohols for constructing cyclopentenones.

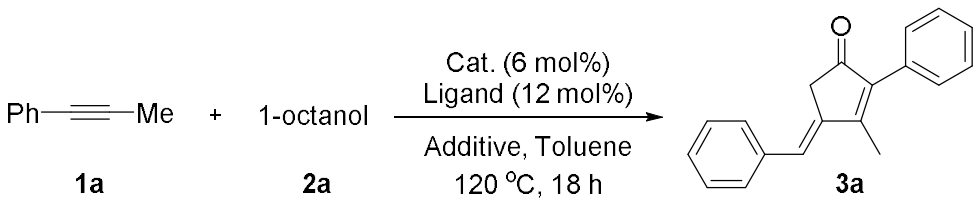
6.2. Results and Discussion

6.2.1. Optimization of the reaction conditions

We initially studied a reaction by mixing the 1-phenyl-1-propyne in the presence of 1-octanol, bis[2-(diphenylphosphino)phenyl]ether (DPEPhos), $InCl_3$, and $[Rh(COD)Cl]_2$ in toluene at 120 °C. The reaction conditions were adopted from the previous work on the Chapter 5. We described our optimizing process of the catalytic reaction below.

At first, phosphines and rhodium sources were screened (Table 6.1). To our surprise, the carbonylative cycloaddition reaction of alkyne was proceeded only in the presence of $[Rh(COD)Cl]_2$/ DPEPhos system. Other catalysts and ligands were inferior to the $[Rh(COD)Cl]_2$/ DPEPhos system. Thus, alcohol was changed from 1-octanol to 4-chlorobenzylalcohol, more reactive species than 1-octanol (Table 6.2). With chlorobenzyl alcohol, the product was obtained 35% yield in the presence of 2 mol% of catalyst and 10 mol% of styrene. We hypothesized that the additive would be able to activate the catalytic cycle. As expected, the catalytic reaction was highly dependent on the temperature (entries 4-7). Having moderate yield of the product in hand, we tested a variety of benzy alcohol and styrene derivatives (Table 6.3). However, the results in Table 6.3 were not better than entry 5 in Table 6.2. Pentafluorobenzyl alcohol gave no product (entry 8). Thus, to improve the reaction yield, other additives were screened (Table 6.4). A variety of additives, such as silver salts, hydride acceptor and Lewis acid, were not good enough.

Table 6.1. Screening reaction conditions with 1-octanol[a]

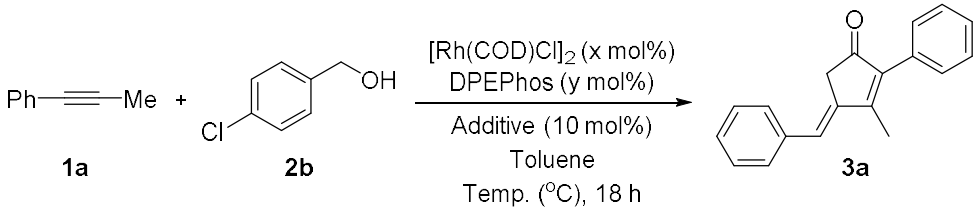


1a **2a** **3a**

entry	cat.	Ligand	Temperature	Yield (%)[b]
1	$Rh(COD)Cl]_2$	dppp	120	No Reaction
2	$Rh(COD)Cl]_2$	dppf	120	N.R.
3	$Rh(COD)Cl]_2$	xantphos	120	N.R.
4	$Rh(COD)Cl]_2$	BINAP	120	N.R.
5	Rh_2OAc_4	DPEPhos	120	N.R.
6	$RhCl_3$	DPEPhos	120	N.R.
7	$[Rh(IMes)(COD)Cl]_2$	DPEPhos	120	N.R.
8	$[Rh(COD)OH]_2$	DPEPhos	120	N.R.
9	$[Rh(CO)_2Cl]_2$	DPEPhos	120	N.R.

[a] Reaction conditions: 0.3 mmol of **2a,** 3 eq. of **1a**, 6 mol% catalyst, 12 mol% of ligand and 2 mL of toluene. [b] Isolated Yield.

Table 6.2. Screening reaction conditions with 4-chlorobenzyl alcohol[a]

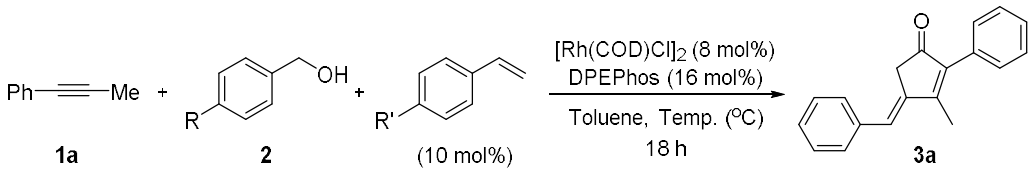


1a **2b** **3a**

entry	cat.	Ligand	Additive	Temperature	Yield (%)[b]
1	2	4	styrene	120	35
2	6	12		120	35
3	6	12	styrene	100	50
4	6	12	styrene	90	39
5	8	16	styrene	100	55
6	8	16	styrene	110	51
7	8	16	styrene	120	35
8	8	16	styrene, H_2O	100	48
9	8	16	*t*-butyl acrylate	100	33
10	8	16		100	42

[a] Reaction conditions: 0.3 mmol of **2b**, 3 eq. of **1a,** x mol% catalyst, y mol% of ligand , 10 mol% of additive and 2 mL of toluene. [b] Isolated Yield.

Table 6.3. Screening reaction conditions with benzyl alcohol derivatives[a]

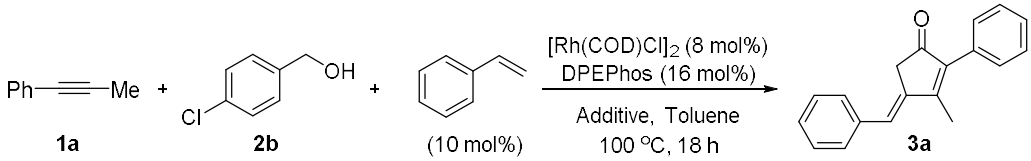


1a **2** (10 mol%) **3a**

entry	R	R'	Temperature	Yield (%)[b]
1	H	OMe	110	49
2	F	H	90	38
3	F	H	100	46
4	F	H	110	41
5	CF_3	H	100	51
6	Cl	Cl	100	49
7	Cl	OMe	100	53
8	F_5	H	100	N.R.

[a] Reaction conditions: 0.3 mmol of **2b**, 3 eq. of **1a,** 8 mol% catalyst, 16 mol% of ligand , 10 mol% of additive and 2 mL of toluene. [b] Isolated Yield.

Table 6.4. Screening reaction conditions with 4-chlorobenzyl alcohol and various additives[a]

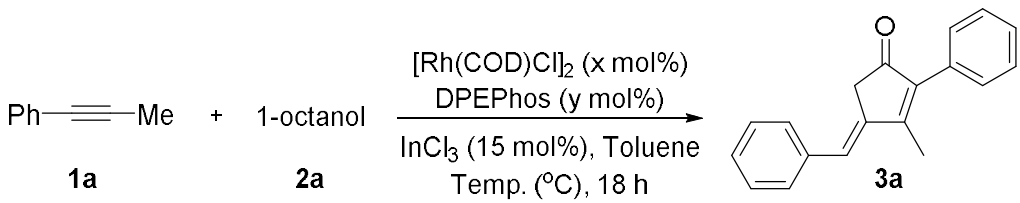


entry	Addtive (20 mol%)	Yield (%)[b]
1	$AgSbF_6$	19
2	$AgBF_4$	Decomposed
3	benzoic acid	Decomposed
4	LiCl	49
5	KI	53
6	$FeCl_3$	trace
7	Mn(0)	49
8	*t*-BuOK	N.R.
9	benzoquinone	trace

[a] Reaction conditions: 0.3 mmol of **2b**, 3 eq. of **1a**, 8 mol% catalyst, 16 mol% of ligand , 10 mol% of styrene, 20 mol% of additive and 2 mL of toluene. [b] Isolated Yield.

As we tried numerous experiments to improve the yield of product, we hypothesized that Lewis acid with less reactive alcohol than 4-chlorobenzyl alcohol will activate the decarbonylation path in the catalytic cycle. Thus, we tested a Lewis acid with 1-octanol (Table 6.5). Under the best conditions, the product was isolated in 76% yield (entry 4). In the optimized conditions in hand, we screened various conditions (Table 6.6). Ligand exchange from DPEphos to Xantphos[19b] and other bidentate phosphines was ineffective (entry 2). Other rhodium compounds like $RhCl_3$ were also examined as catalysts (entry 3). When 1-octanol was replaced with benzyl alcohol, the decomposed product was formed due to the reactivity of benzyl alcohol (entry 4). Interestingly, the use of a CO surrogate, 4-chlorobenzaldehyde,[16] resulted in no desired product (entry 5). Using 1-octanol as a CO surrogate, different additives, varying amounts of catalyst, and different reaction temperatures were explored. Among the additives used ($FeCl_3$, $ZnCl_2$, $Cu(OTf)_2$, and $InCl_3$), the carbonylative [2+2+1] cycloaddition was most favorable in the case of $InCl_3$. Without $InCl_3$, the reaction was sluggish (entry 6), suggesting that $InCl_3$ was a key additive in this reaction. This was not surprising, since it has been reported that $InCl_3$ activates aldehydes to decarbonylation.[23] Other alkynes such as diphenylacetylene showed no activity (entry 7), which implies that the [2+2+1] cycloaddition was specific to 1-phenyl-1-propyne.[22] Addition of hydride acceptors gave no product (entry 8). As expected, no product was formed in the absence of the alcohol, the ligand, or the rhodium catalyst (entries 9–10 and SI). From these results, the optimum conditions were established as follows: 0.3 mmol of 1-octanol, 6 mol% of $[Rh(COD)Cl]_2$, 12 mol% of DPEPhos, 3 equiv. of alkyne, 15 mol% of $InCl_3$, and 2 mL of toluene at 120 °C for 18 h.

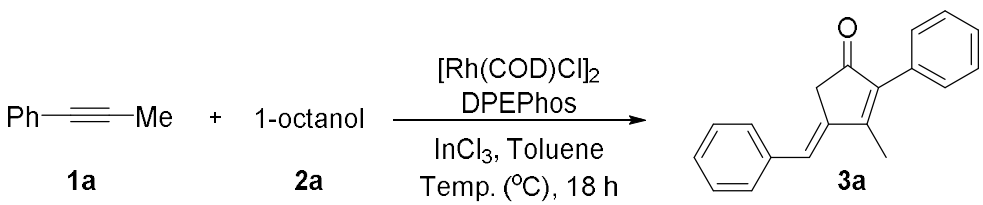
Table 6.5. Screening reaction conditions with 1-octanol and $InCl_3$[a]



entry	cat. (mol %)	Ligand (mol %)	Temperature	Yield (%)[b]
1	8	16	110	40
2	8	16	120	70
3	4	8	120	42
4	6	12	120	76
5	6	12	115	68
6	6	12	125	70

[a] Reaction conditions: 0.3 mmol of **2a**, 3 eq. of **1a**, x mol% catalyst, y mol% of ligand , 15 mol% of $InCl_3$ and 2 mL of toluene. [b] Isolated Yield.

Table 6.6. Variation from standard conditions[a]



1a **2a** **3a**

entry	Variation from standard conditions	Yield (%)[b]
1	None	76
2	Xantphos insead of DPEPhos	N.R.
3	$RhCl_3$ instead of]Rh(COD)Cl]$_2$	N.R.
4	Benzyl alcohol instead of 1-octanol	decomposed
5	4-chlorobenzaldehyde instead of 1-octanol	N.R.
6	Without $InCl_3$	15
7	Diphenylacetylene instead of 1-phenyl-1-propyne	N.R.
8	With 2,6-dichlorobenzoquinone	trace
9	Without [Rh(COD)Cl]$_2$	N.R.
10	Without alcohol	N.R.

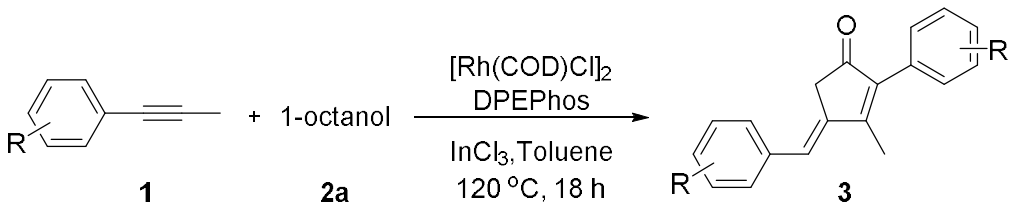
[a] Reaction conditions: 0.3 mmol of **2a**, 3 eq. of **1a**, 6 mol% catalyst, 12 mol% of ligand , 15 mol% of $InCl_3$ and 2 mL of toluene. [b] Isolated Yield. N.R. = No reaction

6.2.2. Substrate Scope and Mechanistic Investigation

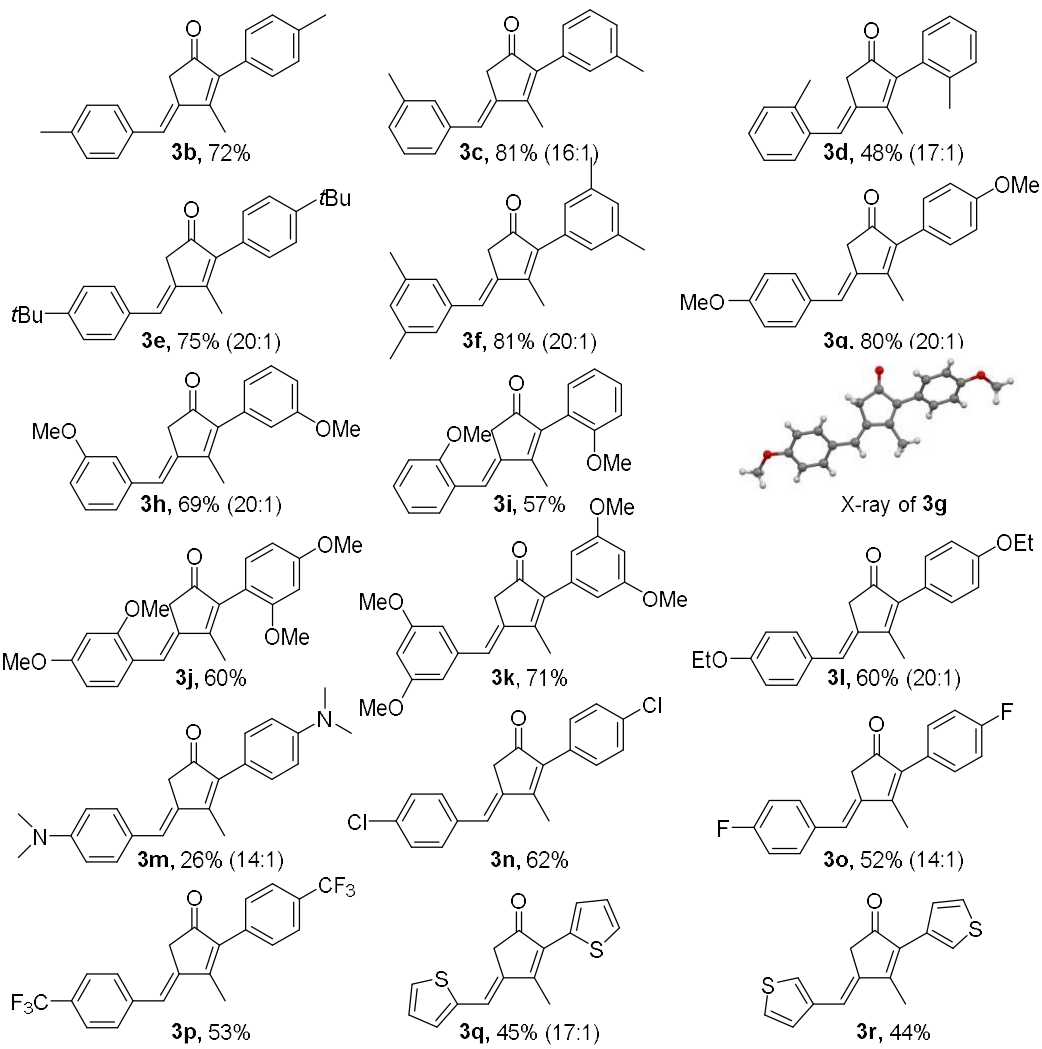
With the optimum reaction conditions established, the substrate scope was studied next (Table 6.7)

Aryl methyl acetylenes with an electron-donating group (Me, OMe, OEt, and *t*-Bu) on the aryl group were found to be good substrates (**3b–3l**). However, a poor yield (26%) was observed for *N*,*N*-dimethyl-4-(1-propynyl)aniline (**3m**). Aryl methyl acetylenes with an electron-accepting group (F, Cl, CF_3) on the aryl group were also studied (**3n–3p**). For substrates bearing F, Cl, or CF_3 groups, reasonable yields (52%, 62%, and 53%, respectively) were observed. In the cases of 2- and 3-(1-propynyl)thiophene (**3q–3r**), reasonable yields (44% and 45%, respectively) were observed. Aryl methyl acetylenes containing a pyridine group did not afford the expected product, presumably due to a side reaction with the rhodium catalyst. Steric effects were observed in some cases; when a methoxy group was located at the *para* or *meta* positions, the corresponding cyclic enones were isolated in 80% and 69%, respectively. However, in the cases of 1-methoxy-2-(prop-1-yn-1-yl)benzene and 2,4-dimethoxy-1-prop-1-yn-1-yl)benzene, reasonable yields (57% and 60%, respectively) were observed. No reaction was observed with 1,3,5-trimethyl-2-(prop-1-yn-1-yl)benzene as the substrate. The regioselectivity was highly dependent upon the substrate. In some cases, a single isomer was isolated, and most of the products were isolated with high regioselectivity (generally > 14:1).

Table 6.7. Scope with various alkyne substrate and 1-octanol[a,b]



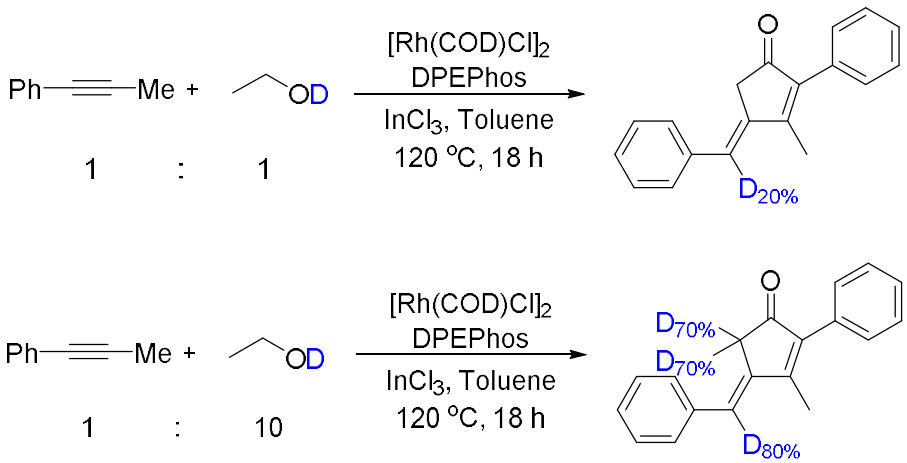
1 2a 3



[a] Reaction conditions: 0.3 mmol of **2a**, 3 eq. of **1**, 6 mol% of $Rh(COD)Cl]_2$, 12 mol% of DPEPhos, 15 mol% of InCl3 and 2 mL of toluene.

[b] Isolated yield. Regioselectivity (E/Z isomer) of products shown in parenthesis

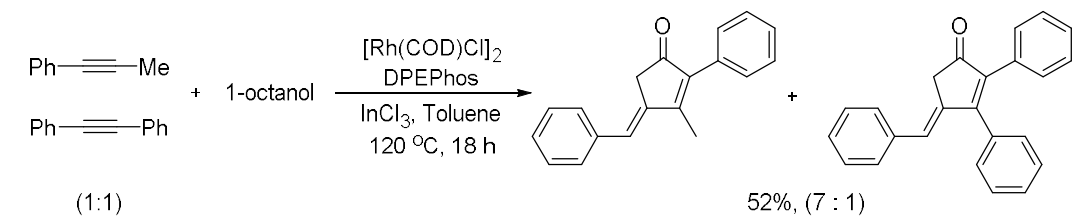
To gain some insight into the possible reaction mechanism, the following reactions were studied. Reaction of 1-phenyl-1-propyne (**1a**) with ethanol-d_1 was studied under the optimized reaction conditions, and the corresponding deuterated product was isolated (Scheme 6.2). The degree and position(s) of deuteration were highly dependent upon the ratio of **1a** to ethanol-d_1. When the ratio was 1:1, the percentage of deuterium incorporated at the benzylidene was 20%. When the ratio was 1:10, 80% of the hydrogens at the benzylidene and 70% of the hydrogens at the C-5 position were replaced by deuterium. These observations suggested the involvement of an Rh-H intermediate and a facile scrambling of the three hydrogens at the benzylic and C-5 positions. Moreover, as the amount of ethanol-d_1 increased, the concentration of metal-deuteride species increased, resulting in high contents of deuterium in various positions in the product.



Scheme 6.2. Carbonylative cycloaddition reaction with ethanol-d_1

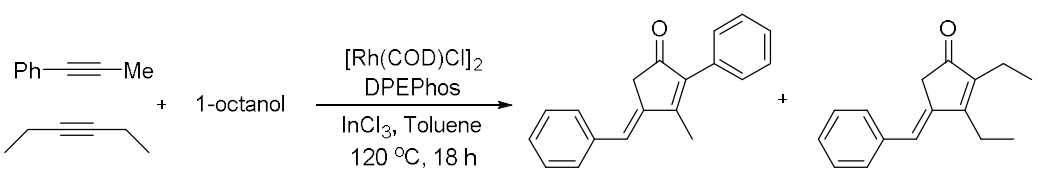
We also performed a competition experiment with various substrates (Scheme 6.3). When a 1:1 mixture of methylphenylethyne and diphenylethyne was used as the substrate, two cyclic enones were isolated in a ratio of 7:1 with 52% yield. The

major product was derived from a carbonylative cycloaddition between methylphenylethynes and the minor product from a carbonylative cycloaddition of methylphenylethyne and diphenylethyne. In the latter case, methylphenylethyne acted as the olefin partner and diphenylethyne as the alkyne. Similar results were obtained from the reaction between methylphenylethyne and dialkyl-ethyne. When a 1:1 mixture of methylphenylethyne and 3-hexyne was used as the substrate, two cyclic enones were isolated in a 4.6:1 ratio with overall 90% yield. In the case of a 1:3 substrate mixture of methylphenylethyne and hept-3-yne, two cyclic enones were isolated in 2.6:1 ratio with overall 87% yield. These observations suggested that an arylmethylethyne, in any combination with other alkynes, could react as both an alkyne and an alkene partner under our conditions, eventually generating cyclic enones. The contribution to the overall yield was not significant but could not be neglected. In some cases, the strategy of combining an arylmethylethyne with other alkynes could be used to prepare specific cyclic enones.



(1:1)

52%, (7 : 1)

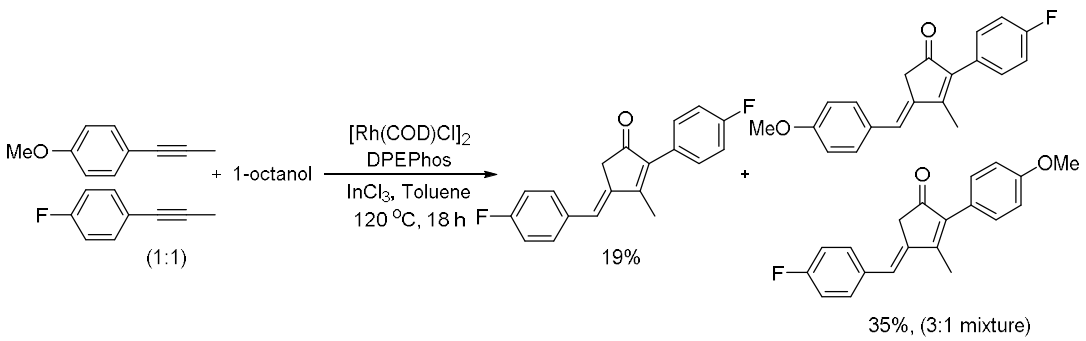


(1:1)

90%, (4.6 : 1)

(1:3)

87%, (2.6 : 1)

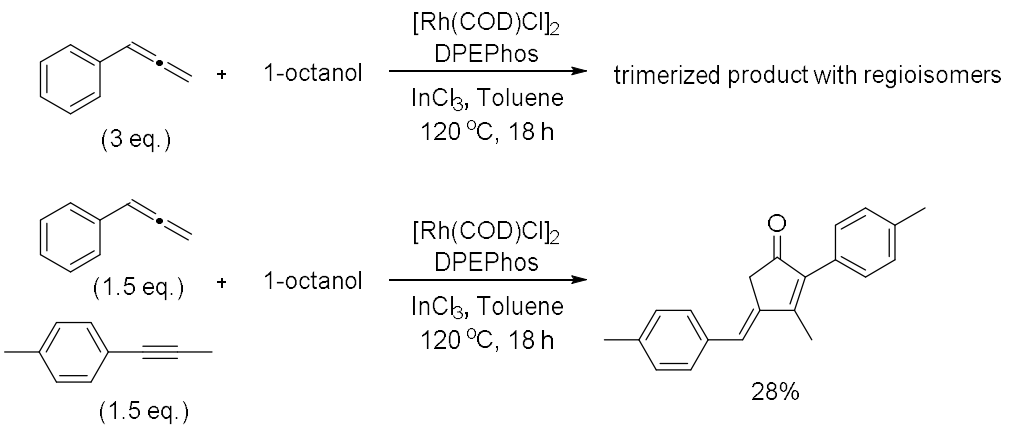


Scheme 6.3. Intercrossing experiment of different alkyne systems

To obtain insight into the electronic effects of functional groups, two alkynes with different electronic effects were tested. When a 1:1 mixture of *p*-methoxy- and *p*-fluoro-substituted methylacetylenes was reacted, 17% of the fluoro-substituted cyclic enone was obtained, while mixed methoxy-fluoro products were obtained in 35% yield with 3:1 ratio. Based on this observation, *p*-fluoro-substituted methylacetylene seems to be a better substrate as an alkyne partner than the *p*-methoxy-substituted one.

Phenylallene has often been suggested as a reaction intermediate in Rh-catalyzed catalytic reactions with 1-phenyl-1-alkyne.[21,22a] Thus, phenylallene was included as a substrate in our reaction (Scheme 6.4). When phenylallene was reacted with 1-octanol, no cyclopentenone was observed. Instead, a trimer of allene with several regioisomers was detected in the GC analysis with 100% conversion (see SI). When a 1:1 mixture of phenylallene and methyl-*p*-tolylethyne was reacted with 1-octanol, a cyclic enone derived from methyl-*p*-tolylethyne was isolated in 28% yield. Thus, phenylallene did not participate in the carbonylative cycloaddition reaction under our reaction conditions.[15c,21] Moreover, this observation suggested that isomerization of methyl-*p*-tolylethyne to 1-methyl-4-(propa-1,2-dien-1-yl)benzene occurred within the coordination sphere of rhodium through the formation of a π-methyl-*p*-tolylethyne rhodium hydride intermediate

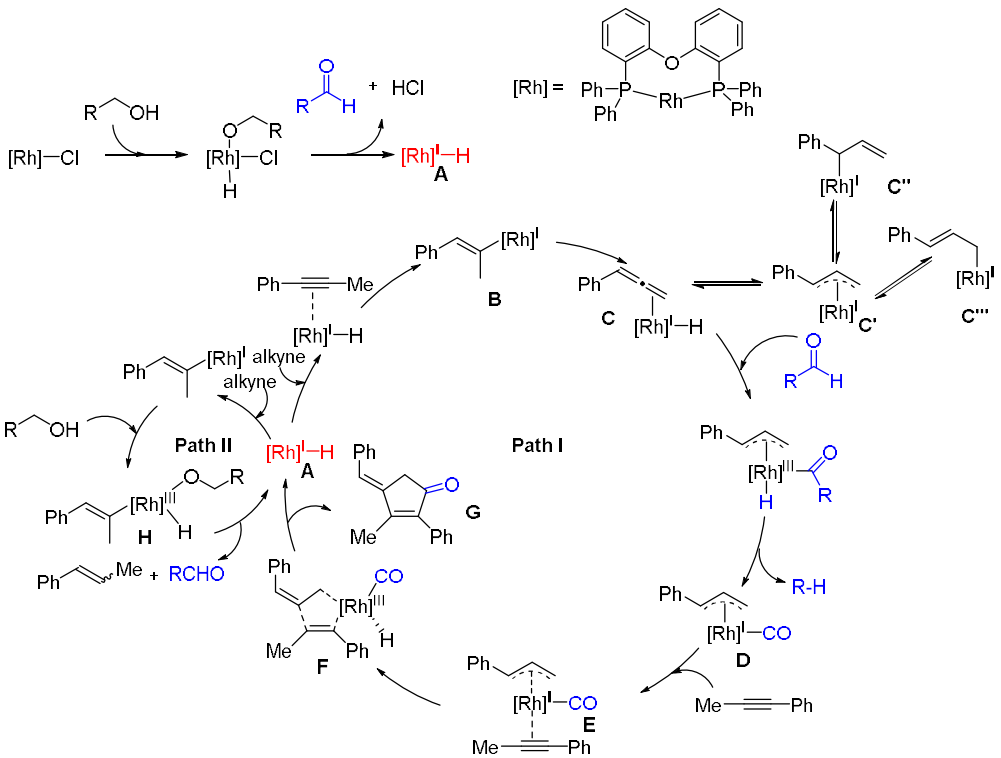
resulting from methyl-*p*-tolylethyne and a rhodium hydride. The rhodium hydride might come from a reaction between the rhodium catalyst and 1-octanol.



Scheme 6.4. Reaction of allene and allene/alkyne

Based on these experimental results, together with observations from previous studies,[17,20,21,22] a plausible reaction mechanism is proposed for the carbonylative [2+2+1] cycloaddition of methylphenylethyne in the presence of a rhodium catalyst, with an alcohol as a CO surrogate (Scheme 5). The reaction begins with the formation of an Rh-H intermediate via a sequential reaction of the rhodium compound with an alkyne and alcohol in Path I. The alkyne is hydrogenated to 1-phenyl-1-propene during the formation of the Rh-H intermediate (**B**). Intermediate (**B**) then isomerizes to form another intermediate π-allene rhodium complex (**C**). The intermediate (**C**) could form an equilibrium mixture with the π-allyl rhodium intermediate (**C'**) and Rh-alkene complexes (**C"** and **C"'**). The π-allyl rhodium intermediate then reacts with an aldehyde to form the rhodium-CO intermediate (**D**). This intermediate (**D**) reacts with another alkyne to form the π-allyl-alkyne rhodium intermediate (**E**). The allyl group acts as an olefin partner in the ring formation of the metallacyclic intermediate (**F**), which then generates products (**G**) and (**A**) by a reductive elimination. The intermediate (**A**) can then enter the catalytic cycle Path II. (**A**) couples with a new alkyne and an alcohol to generate

complex (**H**), which leads to (**A**), an aldehyde, and the hydrogenated product, the alkene. In one example, the generation of the alkene 1-phenyl-1-propene was confirmed by GC analysis. The resulting adduct (**A**) then enters another catalytic cycle.



Scheme 6.5. Reaction of allene and allene/alkyne

6.3. Conclusion

In this study, we have developed an intermolecular [2+2+1] carbonylative cycloaddition of simple alkynes in the presence of an alcohol, $InCl_3$, and an $[Rh(COD)Cl]_2$/DPEPhos catalytic system. The alcohol plays an important role in the formation of cyclopentenones by acting as the source of CO and facilitating the Rh-hydride intermediate. In these transformations, alkynes act as both the olefin and the alkyne partner in the Pauson-Khand type reaction. It is likely that the reaction proceeds via a π-allyl-alkyne rhodium intermediate. Based on the result of mechanistic investigations, the rhodium-hydride species occupies a critical position in the activation of the entire pathway.

6.4. Experimental Section

Materials

All solvents were dried and distilled according to standard methods before use. Solvents utilized in this work were obtained from Sigma-Aldrich and Samchun Pure Chemicals (hexanes, ethyl acetate, dichloromethane, and acetone). Toluene were dried over Na and distilled under nitrogen. *n*-Hexane, diethyl ether, and ethyl acetate were used without further purification. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, or TCI and were used as received. $[Rh(COD)Cl]_2$ were purchased from Pressure Chem. DPEPhos ((oxybis(2,1-phenylene))bis(diphenylphosphane)) and other phosphine ligand were purchased from Alfa Aesar, Sigma-Aldrich and Strem. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254). The TLC plates were visualized by UV-light (254 nm) and treatment with acidic *p*-anisaldehyde and $KMnO_4$ stain followed by gentle heating. Workup procedures were done in air. Flash column chromatography was carried out on Merck 60 silica gel (230 – 400 mesh)

Characterization

^1H and ^{13}C NMR spectra were recorded with Agilent 400-MR DD2 (400 MHz and 100 MHz, respectively) spectrometer. ^1H NMR spectra were taken in $CDCl_3$ and were referenced to residual TMS (7.26 ppm) and reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.00 ppm). High-Resolution Mass Spectra were obtained at the Korea Basic Science Institute (Daegu, South Korea) on a Jeol JMS 700 high resolution mass spectrometer. GC-MS analyses were performed with a HP-6890 series with a

HP-5 capillary column (30 m x 0.25 mm; coating thickness 0.25 μm) and Agilent 5973 Network Mass Selective detector. Analytical condition – initial temperature: 50 ^{o}C, raising temperature 10 ^{o}C / min, final temperature, 280 ^{o}C; He gas: Pressure, 7.56 psi; Total flow: 53.7 mL / min.

Synthesis

Procedure for the preparation of 1-aryl-1-propyne

1-Aryl-1-propynes were prepared according to literature procedure.[24] Phenylallene were prepared according to literature procedure.[13c] Reactions were performed in a schlenk tube equipped with a stirring bar and capped with a rubber septum. The followings were placed in the tube in order: 21.1 mg (c.a. 1 mol%) of Pd, 25.6 mg of dppb (2 mol%), 6 ml of TBAF, 3.0 mmol of 2-butynoic acid. The mixture was stirred at 110 ^{o}C for 3 h. The reaction mixture was extracted with aqueous NH_4Cl solution and diethyl ether. The ether extract was dried over anhydrous $MgSO_4$, filtered, and finally evaporated under reduced pressure. The reaction mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate) to afford the product.

1b: colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 7.9 Hz, 2 H), 7.01 (d, J = 7.8 Hz, 2 H), 2.25 (s, 3 H), 1.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 131.3, 128.9, 120.9, 84.9, 79.7, 21.4, 4.3;HRMS (EI) calc. for $[C_{10}H_{10}, M]^{+}$: 130.0783, found 130.0784

1c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.05 (m, 3 H), 6.99 (d, J = 7.1 Hz, 1 H), 2.23 (s, 3 H), 1.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 132.1, 128.5, 128.4, 128.1, 123.8, 85.4, 79.8, 21.2, 4.3; HRMS (EI) calc. for $[C_{10}H_{10}, M]^{+}$: 130.0783, found 130.0781.

1d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 7.5 Hz, 1 H), 6.51 (d, *J* = 4.1 Hz, 2 H), 6.44 (dd, *J* = 7.8, 4.7 Hz, 1 H), 1.76 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 131.8, 129.2, 127.4, 125.4, 123.8, 89.6, 78.5, 20.7, 4.4; HRMS (EI) calc. for $[C_{10}H_{10}, M]^+$: 130.0783, found 130.0783

1e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 4 H), 1.97 (s, 3 H), 1.23 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 131.1, 125.2, 121.0, 84.9, 79.7, 34.7, 31.2, 4.4; HRMS (EI) calc. for $[C_{13}H_{16}, M]^+$: 172.1252, found 172.1255.

1f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 2 H), 6.87 (s, 1 H), 2.24 (d, *J* = 2.8 Hz, 6 H), 2.00 (d, *J* = 2.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 129.3, 129.1, 123.6, 84.8, 79.9, 21.0, 4.1; HRMS (EI) calc. for $[C_{11}H_{12}, M]^+$: 144.0939, found 144.0937.

1g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2 H), 6.76 – 6.71 (m, 2 H), 3.72 (d, *J* = 0.6 Hz, 3 H), 1.95 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 132.8, 116.2, 113.8, 84.1, 79.4, 55.2, 4.3; HRMS (EI) calc. for $[C_{10}H_{10}O, M]^+$: 146.0732, found 146.0731.

1h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, *J* = 7.9 Hz, 1 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 6.85 (s, 1 H), 6.78 – 6.72 (m, 1 H), 3.70 (s, 3 H), 1.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 129.2, 125.0, 124.0, 116.3, 114.1, 85.7, 79.6, 55.2, 4.3;HRMS (EI) calc. for $[C_{10}H_{10}O, M]^+$: 146.0732, found 146.0732

1i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.5 Hz, 1 H), 7.18 (d, *J* = 6.6 Hz, 1 H), 6.80 (dd, *J* = 14.1, 7.8 Hz, 2 H), 3.81 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 133.6, 128.9, 120.4, 113.0, 110.4, 90.0, 75.8, 55.7, 4.8; HRMS (EI) calc. for $[C_{10}H_{10}O, M]^+$: 146.0732, found 146.0728.

1j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 8.2, 1.6 Hz, 1 H), 6.84 (d, *J* = 1.6 Hz, 1 H), 6.70 (d, *J* = 8.3 Hz, 1 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 1.97 (s, 3 H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 148.8, 148.5, 124.4, 116.2, 114.3, 110.9, 84.1, 79.6, 55.8, 55.8, 4.3; HRMS (EI) calc. for $[C_{11}H_{12}O_2, M]^+$: 176.0837, found 176.0838.

1k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, *J* = 2.3 Hz, 2 H), 6.32 (s, 1 H), 3.68 (d, *J* = 0.5 Hz, 6 H), 1.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 125.3, 109.3, 101.1, 85.5, 79.7, 55.4, 4.3; HRMS (EI) calc. for $[C_{11}H_{12}O_2, M]^+$: 176.0837, found 176.0839

1l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.4 Hz, 2 H), 6.54 (d, *J* = 8.6 Hz, 2 H), 2.87 (s, 6 H), 1.96 (s, 3 H); ^{13}C NMR (100 MHz, $cdcl_3$) δ 149.7, 132.4, 111.9, 111.1, 83.0, 80.2, 40.3, 4.4; m.p. : 79 ^{o}C HRMS (EI) calc. for $[C_{11}H_{13}N, M]^+$: 159.1048, found 159.1046

1m: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2 H), 6.72 (d, *J* = 8.6 Hz, 2 H), 3.94 (q, *J* = 7.0 Hz, 2 H), 1.95 (s, 3 H), 1.33 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 132.8, 116.0, 114.3, 84.0, 79.5, 63.4, 14.8, 4.3; m.p. : 47 ^{o}C, HRMS (EI) calc. for $[C_{11}H_{12}O, M]^+$: 160.0888, found 160.0888

1n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2 H), 7.18 (d, *J* = 8.7 Hz, 2 H), 1.97 (s, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 132.7, 128.5, 122.5, 86.9, 78.7, 4.3; HRMS (EI) calc. for $[C_9H_7Cl, M]^+$: 150.0236, found 150.0234.

1o: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2 H), 6.95 – 6.84 (m, 2 H), 1.95 (s, 3 H); ^{13}C NMR (100 MHz, $cdcl_3$) δ 162.0 (d, *J* = 248.1 Hz), 133.2 (d, *J* = 8.2 Hz), 120.1 (s), 115.4 (d, *J* = 22.0 Hz), 85.4 (s), 78.6 (s), 4.2 (s); HRMS (EI) calc. for $[C_9H_7F, M]^+$: 134.0532, found 134.0530, 133.0456

1p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.2 Hz, 2 H), 7.39 (d, *J* = 8.2 Hz, 2 H), 1.98 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 127.9, 125.1, 125.1, 125.1, 88.7, 78.7, 4.3; HRMS (EI) calc. for $[C_{10}H_7F_3, M]^+$: 184.0500, found 184.0498.

1q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 5.2 Hz, 1 H), 7.03 (d, *J* = 3.4 Hz, 1 H), 6.85 (dd, *J* = 5.1, 3.7 Hz, 1 H), 1.99 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.8, 126.7, 125.8, 124.1, 89.9, 72.9, 4.6; HRMS (EI) calc. for $[C_7H_6S, M]^+$: 122.0190, found 122.0188

1r: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.6 Hz, 1 H), 6.80 – 6.76 (m, 1 H), 6.62 (d, *J* = 5.0 Hz, 1 H), 1.58 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.9, 127.4, 125.0, 122.9, 85.3, 74.8, 4.2; HRMS (EI) calc. for $[C_7H_6S, M]^+$: 122.0190, found 122.0188

Procedure for the entries reported Table 6.7

Reactions were performed in a schlenk tube equipped with a stirring bar and capped with a rubber septum. The followings were placed in the tube in order: 9 mg (c.a. 6 mol%) of catalyst, 19 mg of ligand (12 mol%), 10 mg of $InCl_3$ (15 mol%), 0.3 mmol of 1-octanol , 0.9 mmol of 1-aryl-1-propyne, and 2 mL of toluene. The mixture was stirred at 120 ^{o}C for 18 h. The reaction mixture was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate) to afford the product.

3a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.19 (m, 10 H), 6.71 (s, 1 H), 3.35 (s, 2 H), 2.26 (s, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 164.7, 141.3, 137.2, 136.5, 131.5, 129.4, 129.1, 128.8, 128.2, 128.0, 124.8, 53.4, 39.7, 13.1; IR (ν_{CO}): 1693 cm^{-1}; HRMS (EI) calc. for $[C_{19}H_{16}O, M]^+$: 260.1201, found 260.1199, m. p.: 159 ^{o}C.

3b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.9 Hz, 2 H), 7.15 (dt, *J* = 16.5, 8.0 Hz, 6 H), 6.65 (s, 1 H), 3.30 (s, 2 H), 2.28 (d, *J* = 5.3 Hz, 6 H), 2.23 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 164.5, 140.9, 138.0, 137.7, 136.3, 133.7, 129.5, 129.3, 129.1, 128.9, 128.5, 124.5, 39.7, 21.3, 21.2, 13.1; IR (ν_{CO}): 1698 cm^{-1}; HRMS (EI) calc. for $[C_{21}H_{20}O, M]^+$: 288.1512, found 288.1511, m. p.: 167 ^{o}C.

3c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 4 H), 7.12 – 7.02 (m, 4 H), 6.67 (s, 1 H), 3.34 (s, 2 H), 2.31 (s, 3 H), 2.29 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 164.8, 141.4, 138.3, 137.8, 137.0, 136.4, 131.4, 130.0, 129.9, 128.8, 128.8, 128.7, 128.1, 126.5, 126.3, 124.8, 39.8, 21.5, 13.11, 13.10; IR (ν_{CO}): 1685 cm^{-1}; HRMS (EI) calc. for $[C_{21}H_{20}O, M]^+$: 288.1514, found 288.1511, m. p.: 137 ^{o}C; (*E*/*Z* = 16:1)

3d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 6.1 Hz, 1 H), 7.19 (d, *J* = 4.0 Hz, 2 H), 7.17 – 7.13 (m, 4 H), 6.97 (d, *J* = 7.2 Hz, 1 H), 6.87 (s, 1 H), 3.25 (d, *J* = 3.9 Hz, 2 H), 2.32 (s, 3 H), 2.09 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 165.6, 143.6, 137.8, 137.0, 136.8, 135.2, 131.5, 130.4, 130.2, 129.6, 128.2, 127.9, 127.9, 126.0, 125.6, 122.6, 39.1, 20.0, 19.9, 13.0; IR (ν_{CO}): 1701 cm^{-1}; HRMS (EI) calc. for $[C_{21}H_{20}O, M]^+$: 288.1514, found 288.1514; (*E*/*Z* = 17:1)

3e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 6 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 6.67 (s, 1 H), 3.34 (s, 2 H), 2.26 (s, 3 H), 1.25 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3, 164.6, 151.2, 150.8, 140.8, 136.5, 133.7, 129.1, 129.0, 128.5, 125.7, 125.2, 124.4, 39.8, 34.6, 34.6, 31.2, 31.2, 13.2; IR (ν_{CO}): 1686 cm^{-1}; HRMS (EI) calc. for $[C_{27}H_{32}O, M]^+$: 372.2453, found 372.2454, m. p.: 193 ^{o}C; (*E*/*Z* = 20:1)

3f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2 H), 6.87 (t, *J* = 8.7 Hz, 4 H), 6.62 (s, 1 H), 3.33 (s, 2 H), 2.26 (s, 6 H), 2.25 (s, 6 H), 2.21 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 164.8, 141.5, 138.2, 137.6, 136.8, 136.4, 131.4, 129.7, 129.7, 127.1, 127.1, 124.8, 39.9, 21.3, 21.3, 13.1; IR (ν_{CO}): 1686 cm^{-1}; HRMS (EI) calc. for $[C_{23}H_{24}O, M]^+$: 316.1827, found 316.1826; m. p.: 178 ^{o}C; (E/Z = 20:1)

3g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.3 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 6.87 (m, 4 H), 6.63 (s, 1 H), 3.75 (s, 6 H), 3.30 (s, 2 H), 2.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 164.3, 159.3, 159.2, 140.0, 135.1, 130.7, 130.5, 129.3,

124.0, 114.3, 113.7, 55.3, 55.2, 39.7, 13.2; IR (ν_{CO}): 1690 cm^{-1}; HRMS (EI) calc. for $[C_{21}H_{20}O_3, M]^+$: 320.1412, found 320.1413, m. p.: 162 °C; (*E*/*Z* = 20:1)

3h: ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2 H), 6.99 (d, *J* = 7.7 Hz, 1 H), 6.93 (s, 1 H), 6.89 – 6.77 (m, 4 H), 6.69 (s, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.36 (s, 2 H), 2.27 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 164.9, 159.8, 159.4, 141.4, 137.8, 137.4, 132.8, 129.7, 129.3, 124.9, 121.9, 121.8, 115.0, 114.4, 113.8, 113.7, 55.3, 55.2, 39.7, 13.2; IR (ν_{CO}): 1696 cm^{-1}; HRMS (EI) calc. for $[C_{21}H_{20}O_3, M]^+$: 320.1412, found 320.1415; m. p.: 121 °C; (*E*/*Z* = 20:1)

3i: ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.5 Hz, 1 H), 7.30 – 7.16 (m, 3 H), 7.08 (s, 2 H), 6.95 – 6.84 (m, 4 H), 3.82 (d, *J* = 2.5 Hz, 3 H), 3.72 (d, *J* = 2.5 Hz, 3 H), 3.30 (s, 2 H), 2.12 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 167.0, 157.4, 157.0, 139.5, 137.5, 131.1, 129.6, 129.2, 128.8, 125.6, 120.9, 120.6, 120.4, 118.8, 111.1, 110.7, 55.54, 55.46, 39.6, 13.6; IR (ν_{CO}): 1697 cm^{-1}; HRMS (EI) calc. for $[C_{21}H_{20}O_3, M]^+$: 320.1412, found 320.1413

3j: ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.3 Hz, 1 H), 6.95 (s, 1 H), 6.85 (m, 4 H), 6.64 (s, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.83 (s, 6 H), 3.35 (s, 2 H), 2.28 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 164.5, 149.0, 149.0, 148.8, 148.6, 140.2, 135.1, 129.6, 124.4, 124.2, 122.6, 122.2, 112.6, 111.7, 111.2, 110.9, 55.9, 55.84, 55.82, 55.79, 39.7, 13.2; IR (ν_{CO}): 1695 cm^{-1}; HRMS (EI) calc. for $[C_{23}H_{24}O_5, M]^+$: 380.1624, found 380.1624; m. p.: 182 °C.

3k: ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1 H), 6.52 (d, *J* = 2.1 Hz, 2 H), 6.41 (d, *J* = 2.2 Hz, 2 H), 6.38 (d, *J* = 2.2 Hz, 1 H), 6.33 (s, 1 H), 3.71 (s, 6 H), 3.71 (s, 6 H), 3.31 (s, 2 H), 2.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 165.0, 160.8, 160.5, 141.5, 138.1, 137.4, 133.2, 125.0, 107.5, 107.1, 100.3, 100.1, 55.3, 39.6, 13.1; IR (ATR): 1690 cm^{-1}; HRMS (EI) calc. for $[C_{23}H_{24}O_5, M]^+$: 380.1624, found

380.1620; m. p.: 153 °C.

3l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 6.86 (m, 4 H), 6.63 (s, 1 H), 3.99 (q, *J* = 7.0 Hz, 4 H), 3.31 (s, 2 H), 2.25 (s, 3 H), 1.35 (td, *J* = 6.9, 1.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 164.3, 158.7, 158.6, 140.0, 135.0, 130.8, 130.6, 129.2, 124.0, 123.8, 114.8, 114.3, 63.5, 63.4, 39.8, 14.8, 13.2, 13.2; IR (ν_{CO}): 1695 cm^{-1};HRMS (EI) calc. for [$C_{23}H_{24}O_3$, M]$^+$: 8.1725, found 348.1725; m. p.: 150 °C; (*E*/*Z* = 20:1)

3m: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2 H), 7.25 (d, *J* = 8.6 Hz, 2 H), 6.73 (d, *J* = 8.3 Hz, 2 H), 6.65 (d, *J* = 8.6 Hz, 2 H), 6.58 (s, 1 H), 3.32 (s, 2 H), 2.93 (s, 6 H), 2.91 (s, 6 H), 2.26 (s, 3 H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 204.0, 163.7, 149.7, 139.3, 133.2, 130.5, 130.3, 130.1, 125.0, 124.0, 119.8, 112.2, 112.0, 40.4, 40.18, 40.15, 13.3; IR (ν_{CO}): 1687 cm^{-1}; HRMS (EI) calc. for [$C_{23}H_{26}ON_2$, M]$^+$: 346.2045, found 346.2043; m. p.: 228 °C; (*E*/*Z* = 14:1)

3n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 6 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 6.69 (s, 1 H), 3.32 (s, 2 H), 2.26 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 164.7, 140.5, 137.5, 134.8, 134.1, 134.0, 130.8, 130.3, 129.7, 129.1, 128.6, 124.0, 39.5, 13.2; IR (ν_{CO}): 1701 cm^{-1}; HRMS (EI) calc. for [$C_{19}H_{14}OCl_2$, M]$^+$: 328.0422, found 328.0424; m. p.: 208 °C

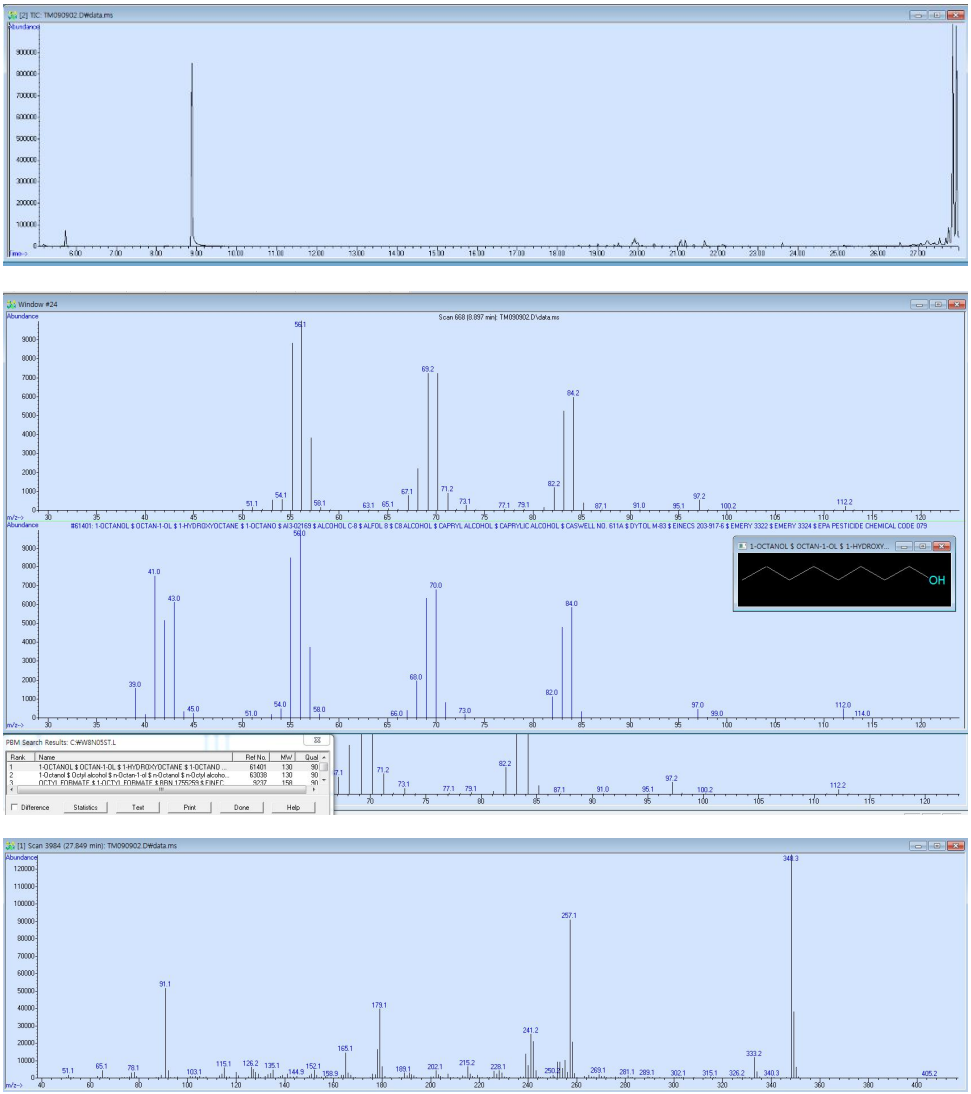
3o: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2 H), 7.29 (m, 2 H), 7.04 (m, 4 H), 6.69 (s, 1 H), 3.31 (s, 2 H), 2.25 (s, 3 H); ^{13}C NMR (100 MHz, cdcl$_3$) δ 202.6 (s), 164.6 (s), 163.6 (d, *J* = 16.3 Hz), 161.1 (d, *J* = 18.0 Hz), 140.3 (s), 136.7 (s), 132.6 (s), 131.3 (d, *J* = 8.1 Hz), 130.8 (d, *J* = 8.0 Hz), 127.4 (s), 123.8 (s), 115.9 (d, *J* = 21.6 Hz), 115.4 (d, *J* = 21.5 Hz), 39.4 (s), 13.1 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.46, -113.18; IR (ν_{CO}): 1678 cm^{-1}; HRMS (EI) calc. for [$C_{19}H_{14}OF_2$, M]$^+$: 296.1013, found 296.1013; m. p.: 182 °C; (*E*/*Z* = 14:1)

3p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 4 H), 7.50 (m, 2 H), 7.43 (m, 2 H), 6.79 (s, 1 H), 3.37 (s, 2 H), 2.30 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 165.1, 141.0, 139.7, 139.2, 134.9, 129.8, 129.3, 125.8, 125.7, 125.3, 125.2, 124.1, 39.4, 13.1; IR (ν_{CO}): 1701 cm^{-1}; HRMS (EI) calc. for $[C_{21}H_{14}OF_6, M]^+$: 396.0949, found 396.0948; m. p.: 192 ^{o}C

3q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 3.7 Hz, 1 H), 7.42 – 7.32 (m, 2 H), 7.14 – 7.07 (m, 2 H), 7.02 (dd, *J* = 5.0, 3.7 Hz, 1 H), 6.98 (s, 1 H), 3.31 (s, 2 H), 2.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 161.2, 141.0, 135.2, 134.0, 133.1, 129.5, 128.2, 128.0, 127.7, 127.2, 127.0, 118.2, 39.6, 13.6; IR (ν_{CO}): 1685 cm^{-1}; HRMS (EI) calc. for $[C_{15}H_{12}OS_2, M]^+$: 272.0330, found 272.0332; m. p.: 171 ^{o}C; (*E*/*Z* = 17:1)

3r: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1 H), 7.31 (m, 4 H), 7.18 (m, 1 H), 6.76 (s, 1 H), 3.28 (s, 2 H), 2.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 163.2, 138.5, 136.0, 135.9, 131.9, 127.9, 127.7, 126.3, 125.6, 125.3, 125.1, 118.5, 39.8, 13.3; IR (ν_{CO}): 1694 cm^{-1}; HRMS (EI) calc. for $[C_{15}H_{12}OS_2, M]^+$: 272.0330, found 272.0331; m. p.: 135 ^{o}C.

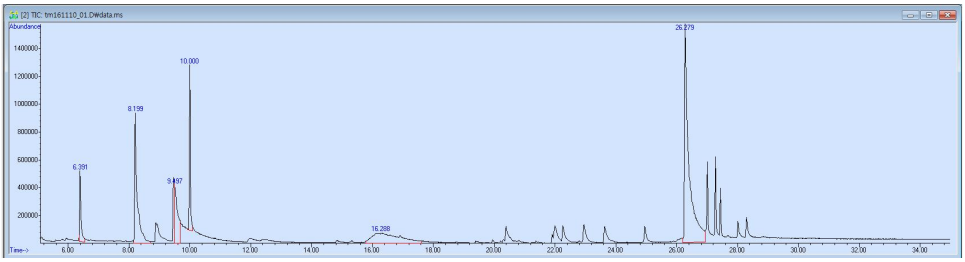
6.5. Supporting Information

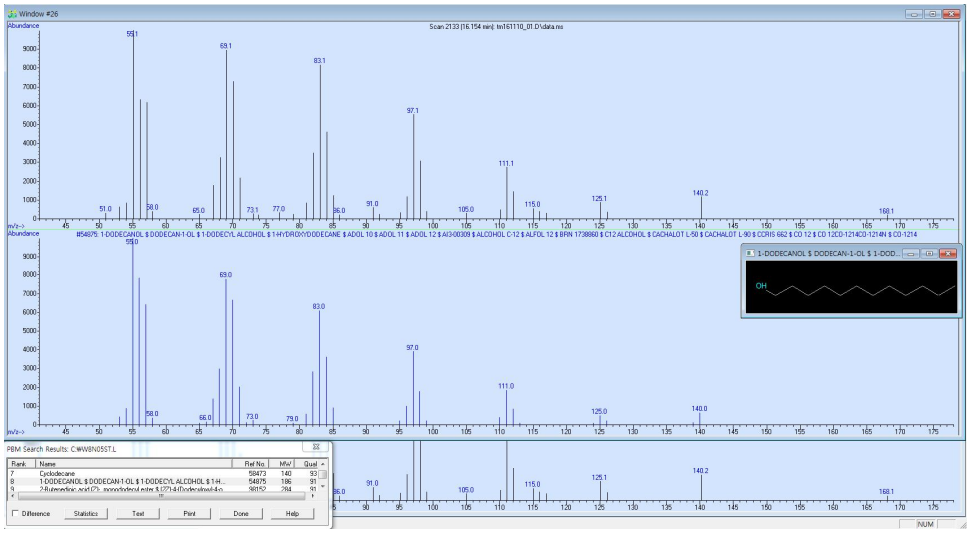


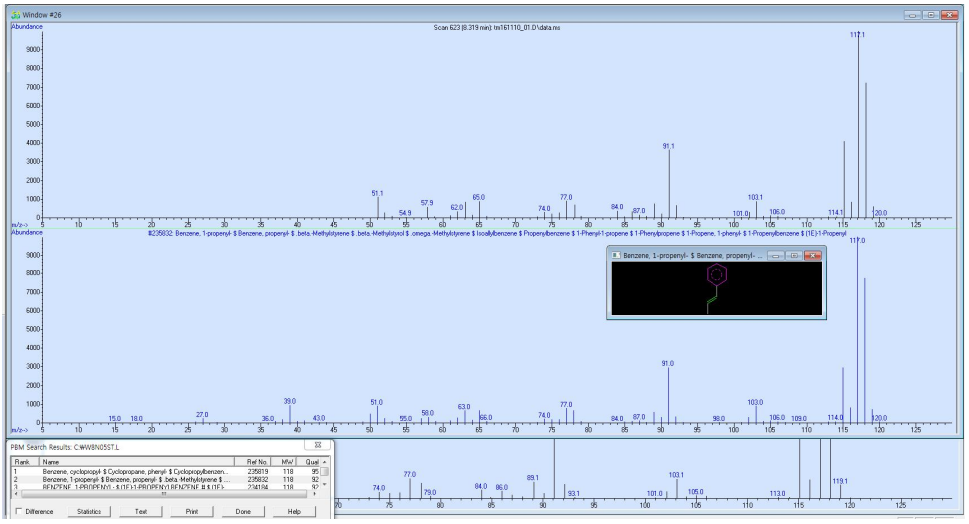
8.9 min : 1-octanol (unreacted)

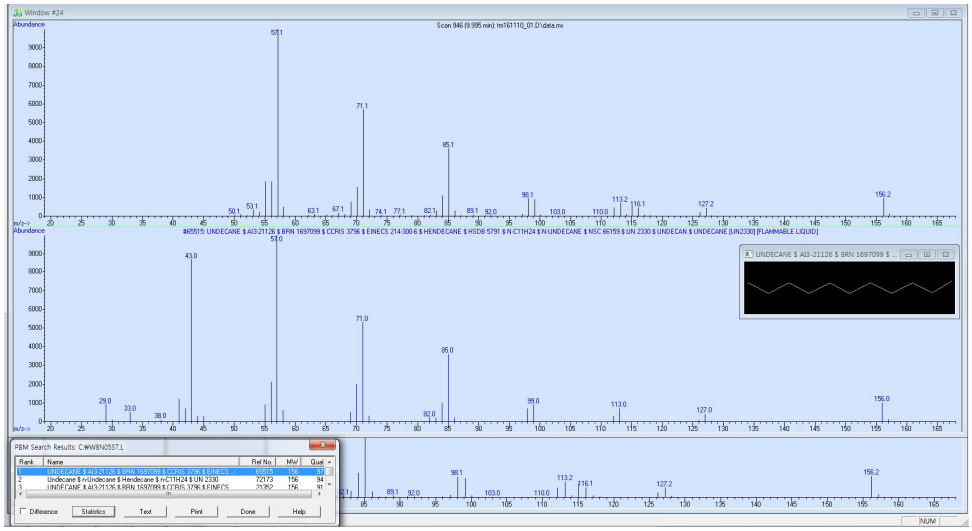
27 ~ 28 min : unidentified trimerized regioisomer

Figure S6.1. GC analysis of Scheme 6.4


[2] TIC: tm161110_01.Dwdata.ms
Abundance
Time-->
6.391
8.199
9.997
10.000
16.288
26.279


Window #26
Scan 2133 (16.154 min): tm161110_01.D\data.ms
Abundance
m/z-->
55.1
69.1
83.1
97.1
111.1
125.1
140.2
#58675: 1-DODECANOL $ DODECAN-1-OL $ 1-DODECYL ALCOHOL $ 1-HYDROXYDODECANE $ ADOL 10 $ ADOL 11 $ ADOL 12 $ AI3-00309 $ ALCOHOL C-12 $ ALFOL 12 $ BRN 1738860 $ C12 ALCOHOL $ CACHALOT L-90 $ CACHALOT L-90 $ CCRIS 662 $ CO-12 $ CO 12CO-1214CO-1214N $ CO-1214
1-DODECANOL $ DODECAN-1-OL $ 1-DOD...
OH
PBM Search Results: C:\W6N05ST.L
Rank
Name
Ref No.
MW
Qual
7 Cyclododecane 59472 140 93
8 1-DODECANOL $ DODECAN-1-OL $ 1-DODECYL ALCOHOL $ 1-H... 54875 186 91
9 2-Buteneacid, ester with 2-methyl-1-propanol 98152 284 91
Difference
Statistics
Text
Print
Done
Help
NUM


Window #26
Scan 623 (8.319 min): tm161110_01.D\data.ms
Abundance
m/z-->
117.1
91.1
#235832: Benzene, 1-propenyl- $ Benzene, propenyl- $ .beta.-Methylstyrene $ .beta.-Methylstyrol $ .omega.-Methylstyrene $ Isoallylbenzene $ Propenylbenzene $ 1-Phenyl-1-propene $ 1-Phenylpropene $ 1-Propene, 1-phenyl- $ 1-Propenylbenzene $ (1E)-1-Propenyl
Benzene, 1-propenyl- $ Benzene, propenyl- ...
PBM Search Results: C:\W6N05ST.L
Rank
Name
Ref No.
MW
Qual
1 Benzene, cyclopropyl- $ Cyclopropane, phenyl- $ Cyclopropylbenzen... 235819 118 95
2 Benzene, 1-propenyl- $ Benzene, propenyl- $ .beta.-Methylstyrene $ ... 235832 118 92
3 BENZENE, 1-PROPENYL-, (1E)-1-PROPENYLBENZENE $ (1E)-... 274184 118 92
Difference
Statistics
Text
Print
Done
Help



6.3 min : 1,5-Cyclooctadiene

8.2 min : 1-propenyl benzene

9.4 min : 1-phenyl-1-propyne (substrate)

10.00 min : undecane

16.28 min : 1-dodecanol

26.27 min : product

Figure S6.2. GC analysis of Scheme 6.5

6.6. References

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국문초록

전이금속을 이용한 촉매반응은 화학결합을 만드는 데 있어서 가장 근본적인 방법 중 하나이다. 전이금속 촉매의 형태에 따라, 촉매의 반응성은 매우 다르다. 불균일화 촉매의 영역에서, 나노입자 촉매는 특이한 반응성과 상대적으로 쉬운 재사용 방법 덕분에 많은 관심을 받고 있다. 균일화 촉매 또한 높은 반응성과 정밀화학에서의 높은 선택성 등의 장점을 가지고 있따. 따라서, 전이금속 촉매를 이용해서 독특한 촉매반응을 개발하는 것은 새로운 합성방법을 넓히는 데 필수적이다.

본 연구에서는 전이금속 나노입자 촉매와 로듐 화합물을 이용해 새로운 촉매반응을 개발하였다. 우리는 활성화 되지 않은 차콜에 입힌 루테늄 나노입자 촉매가 색을 내는 물질인 염료 등에 유용한 아조벤젠 유도체 들을 합성하는데 효과적인 것을 발견했다. 게다가, 수소 기체를 사용하는 대신 에탄올이 수소 공급원으로 사용되는 것을 알아냈다. 반응조건인 에탄올의 양을 조절함으로써 니트로아렌 계열의 물질에서부터 세 가지 다른 화합물을 선택적으로 합성할 수 있었다.

구리는 루테늄 보다 양도 많고 값도 싼 금속이다. 우리는 상업적으로 이용 가능한 구리 나노입자를 촉매로 사용해서 알킬 할라이드 와 그리냐드 화합물 간의 교차 결합 반응을 연구했다. 이러한 촉매반응은 포스핀 이나 아민 등의 리간드가 필요하지 않고, 상온이라는 매우 온화한 조건에서 반응이 진행되었다. 특히, 4차 탄소 중심과 같이 합성하기 어려운 구조를 구리 나노입자 촉매와 3차 그리냐드 화합물 하에서 합성할 수 있었다.

알코올은 우리 생활에서 쉽게 찾아볼 수 있는 유기화합물 이다. 보통 화학반응에서 극성 용매로 주로 쓰인다. 위에서 언급한 바와 같이 알코올은 수소공급원으로 사용될 수 있다. 게다가, 알코올은 로듐 촉매 하에서 수소 공급원 뿐만 아니라 일산화탄소 대체제, 하이드라이드 공급원 그리고 친핵체 역할까지 할 수 있다는 것을 발견했다. 아릴 요오드 화합물과 알코올은 로듐 촉매 하에서 에스터 화합물을 만드는데, 이 반응에서 알코올은 일산화탄소 와 친핵체 역할을 한다. 또한 알코올은 로듐 촉매와 알카인 이 존재할 때 분자간 일산화탄소를 첨가하는 고리화 반응에서 로듐-하이드라이드 를 만들어주면서 일산화탄소 공급원의 역할도 같이 수행한다.

주요어: 나노입자 촉매, 루테늄, 수소화반응, 구리, 교차결합 반응, 로듐, 알코올, 일산화탄소 반응, 고리화 반응

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